Field-Deployable 'Dry Component' Approach to Resuscitation for Hemorrhagic Shock

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Disclosures

- Company Interest
  - I am an employee of **KaloCyte, Inc.** with stock options. **(ErythroMer®)**
- Funding
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  - NIH/NHLBI STTR: R42HL135965

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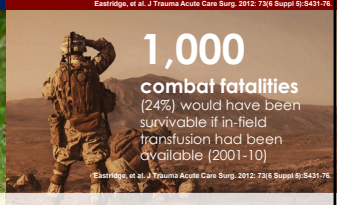
The Problem: High Mortality from Blood Loss after Traumatic Injury

In **civilian trauma**, hemorrhage is responsible for ~ 35% of pre-hospital deaths.
Kauvar, et al. J Trauma. 2006; 60, S3-11.

25,000
preventable deaths due to hemorrhage after injury occur per year in the U.S.
Yazer, et al. Vox Sang. 2018; 113(7):701-706.

Hemorrhage accounts for ~ 90% of potentially survivable **battlefield deaths**
Eastridge, et al. J Trauma Acute Care Surg. 2012; 73(6 Suppl 5):S431-76.



1,000
combat fatalities (24%) would have been survivable if in-field transfusion had been available (2001-10)
Eastridge, et al. J Trauma Acute Care Surg. 2012; 73(6 Suppl 5):S431-76.

MINUTES MATTER: Every minute of delay in replacing lost blood increases mortality by **5%**
Meyer, et al. J Trauma Acute Care Surg. 2017; 83, 19-24.

2

Unmet Needs

Blood loss is the **LEADING CAUSE** of preventable death after trauma, but stored blood is not always an immediate option.

A WHOLE BLOOD SUBSTITUTE IS NEEDED
when stored blood and blood components are:

unavailable

- **Pre-hospital** (ambulances, scene rescue)
- **Austere settings** (battlefield, ships, remote missions)
- **Developing world** (inadequate donor pool & blood banking resources)

undesirable

- Emergency use of **un-cross matched blood**
- Priming **cardiopulmonary bypass** circuits
- Avoidance of **immune responses**

in short supply

- **Mass casualty events**
- Acute Radiation Syndrome

ALL PRIOR HBOC & PFC ATTEMPTS HAVE FAILED TO OBTAIN FDA LICENSURE

Poor O_2 delivery
(capture oxygen (O_2) in lung, but do not release O_2 to tissue)

Vasospasm
(sequester nitric oxide (NO), an endogenous vasodilator)

3

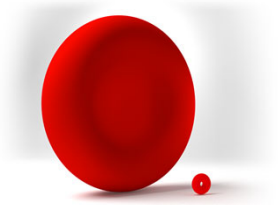
ErythroMer: Dried, Bio-inspired Artificial RBC

ErythroMer provides a bridge to hospital-based blood transfusions

Nano-encapsulated human hemoglobin
- Bioengineered to **mimic RBC physiology**
- Toroidal "donut" shape maximizes surface area
- Context-sensitive oxygen affinity

Synthetic nanoparticle structure
- Does not require blood typing; **universal option**
- Benign interaction with vasculature
- Clears rapidly from bloodstream (~3-7h)

Freeze dried or lyophilized
- Amenable to **long-term dry storage** at ambient conditions
- **Lightweight**; **no cold chain** required
- Easily reconstituted and administered



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ErythroMer In Vivo Efficacy
(hemodilution, HIF-bioluminescence, mice)

Manipulation:	70% vol X (HES)	30% vol X (EM)	-	-	-
Murine RBC [Hb]:	5	4	4	4	5
EM [Hb]:	0	10	2	0	0

* latest version has extended half-life

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Hemodilution model in HIF-bioluminescence reporter mice demonstrates ErythroMer's efficacy as an oxygen carrier

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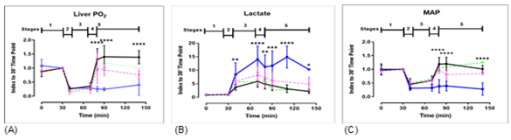
ErythroMer Normalizes Oxygenation
(Hemorrhagic Shock model: Non-inferiority to Blood)

Normalized Results of Parameters During Shock Resuscitation With Different Substitutes: Oxygenation/Acute Shock Studies Data



Stages: 1 – Baseline; 2 – Hemorrhage/Shock Induction; 3 – Shock; 4 – Resuscitation/Infusion; 5 – Post-resuscitation

Resuscitation Fluid:
Black: Blood n=6
Blue: Albumin n=4
Light green: 100 *10^9 (EM circ. conc.) n=1
Rose pink: 300 *10^9 (EM circ. conc.) n=4

*circ. conc. stands for circulating concentration

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Developmental Landscape for Whole Blood: Hemostatic Components

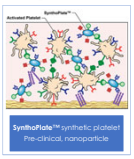
Teleflex | Cellphire | haima therapeutics

Freeze-Dried Plasma
BLA expected early 2019, accelerated approval

- Submitted grant collaboration

Thrombosome® Freeze-Dried Platelets
Phase 1 trials, BARDA contract

- Existing grant collaboration



SynthoPlate™ synthetic platelet
Pre-clinical, nanoparticle

- Submitted grant collaboration

KaloCyte plans to test for compatibility with other freeze-dried or synthetic blood components in development

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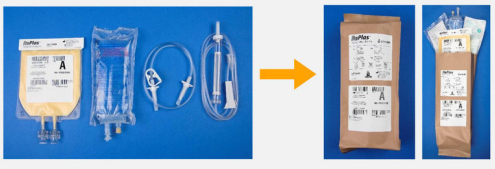
Teleflex – Freeze Dried Plasma (FDP)



Teleflex

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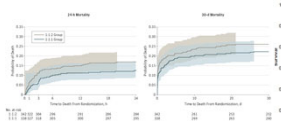
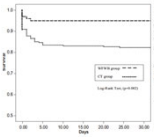
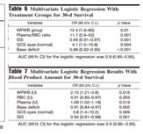
Transfusion Component Composition (for Hemorrhagic Shock) Influences Outcome

Transfusion of Plasma, Platelets, and Red Blood Cells in a 1:1:1 vs a 1:1:2 Ratio and Mortality in Patients With Severe Trauma. (PROPPR)
JAMA. 2015;313(5):471-482.



Warm fresh whole blood is independently associated with improved survival for patients with combat-related trauma
J Trauma. 2009;66:S69-76.





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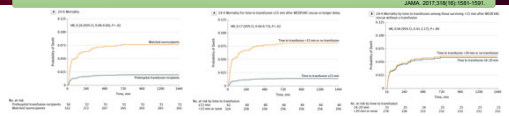
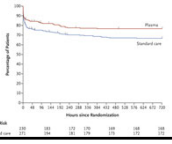
Transfusion Timing for Hemorrhagic Shock Influences Efficacy

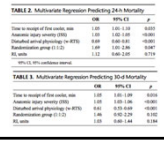
Association of Prehospital Blood Product Transfusion During Medical Evacuation of Combat Casualties in Afghanistan w/ Acute & 30d Survival
JAMA. 2017;318(16):1581-1591.



Prehospital Plasma (PAMPer) Air Transport for Penetrating Trauma & Hemorrhagic Shock
NEJM.2018;379(4):315-326.

Every minute counts: Time to delivery of initial massive transfusion cooler and its impact on mortality.
J Trauma. 2017; 83(1):19-24.





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What have we learned (simply put)?

- Put it back the way you found it.
- Take care of the minutes, and the hours will take care of themselves.

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Needs for Pragmatic Implementation

Field-Deployable 'Dry Component' Approach to Hemostatic Resuscitation

- Biocompatibility Amongst Components
- Pharmacokinetics & Pharmacodynamics
- Packaging & Delivery Systems
- Dosing & Administration Strategy
- Benchmarking in Suitable Models
- Human Trials with Meaningful Outcomes
- Optimize Regulatory Efficiency

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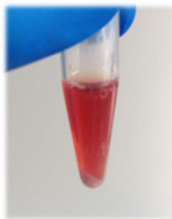
Lightweight, Portable, Temperature-Stable Option for Rapid, Easy Reconstitution and Administration



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HBOC Field Historical Perspective

Table 3	Current Status of Blood Substitute Field				
Product	AKA	Company	Hb	Modification	State of Development
HemAssist	Diasperin-croslinked Hb (DCLHb)	Baxter	Human	diasperin α-α crosslinked tetramer	Phase III cardiac surgery, ANH, trauma/stroke, Stopped in 2008
HemoLink	Hemoglobin raffimer	Hemosol	Human	Intra- and inter-molecular crosslinking with O-raffinose	Phase III surgery, ANH, cardiac surgery Stopped in 2004
Hemopure	Hemoglobin glutamer-250	OPK Biotech	Bovine	Gluteraldehyde polymerization	Phase III surgery, ANH, cardiac surgery FDA denied further trials in 2008. Appr for adult use So Africa & Russia.
Optpro	rHb1.1	Somatogen	Recombinant	Intramolecular crosslinked at β chain mutation (βlys[108])	Phase II, stopped in 1999
PEG-Hb		Enzon	Bovine	Polyethylene glycol (PEG) conjugated	Phase IIb, tumor radiosensitization, stopped 1996
Hemoximer	PHP	Curacyte	Human	Surface modified polyoxylethylene pyroxilated polymer	Phase III, distributive shock, intended to trap NO, stopped 2009
PolyHeme		Northfield	Human	Gluteraldehyde polymerization	Phase III, trauma, surgery Stopped in 2009
Hemospan	MP4	Sangart	Human	Maleimide-Polyethylene-Glycol modified	Phase III completed in Europe, Suspended 2010
OxyVita	Zero-link Hb (ZI-Hb)	OxyVita	Human	Very large Hb polymer (25MD)	Pre-clinical (USN CRADA), near vet use
Hem-M101	Hemoxycarrier	Hemarina	Marine worm	megaHb (156 linked globins)	Pre-clinical, not at scale up
VitalHeme	Polynitroxylated Pegylated Hb	SynZyme	Bovine	14 nitroxide & 8-10 PEG moieties	Pre-clinical, not at scale up
HbV	Hemoglobin Vesicles	WABIOS	Human	Liposome-encapsulated Hb	Pre-clinical, not at scale up
	Various polymeric nanoparticles	-	Bovine/Human	PEG-PLA shell, complex metHb reduction systems	Pre-clinical, not at scale up
FluosolDA			none	Perflorocarbon emulsion	Phase III cardiac surgery, stopped 2001
Oxygent	Perflubron	Alliance	none	Perflurocarbon emulsion	Phase III surgery, stopped 2008
Oxyfluor		Hemogen	none	Perflurocarbon / lipid emulsion	Pre-clinical, stopped 2007

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Current RBC Substitute Landscape

Product (Company)	Category	Oxygen capture & release	Designed to prevent NO trapping & vasospasm	Storage temp, shelf life	Physical Form	Development Status & Availability
Stored Blood (whole or pRBCs)	**Human Blood / blood products**	**Context-sensitive**	**Yes**	**Refrigeration, 42 days**	**Liquid**	**Approved, available via blood suppliers**
PolyHeme (Northfield Labs)	HBOC – chemically modified Hb	Fixed	No	Refrigeration, prolonged	Liquid	Phase III trauma trial stopped in 2009
Hemopure (HbO2 Therapeutics)	HBOC: Polymerized bovine Hb	Fixed	No	Ambient, prolonged	Liquid	FDA denied new trials. Approved in Russia, South Africa
HEMOXYCarrier (Hemarina)	HBOC: Extracellular marine invert Hb	Fixed	No	Refrigeration, prolonged	Liquid	Phase I, organ preservation
DDFPe (NuvOx)	PFC: Dodecafluoro-pentane emulsion	Fixed	No	Ambient, prolonged	Liquid	Phase II, stroke
ErythroMer (KaloCyte)	Nano-encapsulated human Hb	Context-sensitive	Yes	Ambient, prolonged	Dried	Pre-clinical, traumatic hemorrhagic shock

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