

Hemoglobin Oxygen Therapeutics LLC

**The world leader in life preserving oxygen
carrying solutions**

March 2021

Investor Presentation

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Mission Statement

To develop and commercialize the first and best in class technology platform for oxygen-carrying solutions addressing critical unmet medical needs in human and veterinary indications.

Company at a Glance

Delaware registered in 2014, technology is going back to 1990s with \$1 billion invested
\$20 million in equity financing to date

Acquired and developed the intellectual property for two Hemoglobin-Based Oxygen Carrier (HBOC) products :

- Hemopure (HBOC-201) for human use
- Oxyglobin (HBOC-301) for veterinary use

Existing collaborations in veterinary and human markets

Groundbreaking HBOC organ perfusion technology

Currently 12 employees

Production facility in Souderton, Pennsylvania

Highly experienced team

Zaf Zafirelis

Co-Founder & CEO



30 years of Biotech, Pharma, and Medical Device industries
More than 20 years CEO experience
Raised more than \$100 million with successful exits

Joseph Rappold, MD

Chief Medical Officer



30 years of active service (US Navy) with 6 combat deployments commanding a variety of medical facilities. Professor of Surgery at Tufts University. Chief of Acute Care Surgery and Trauma Medical Director at Maine Medical Center.

Greg Dube, PhD

VP, Research & Development



30 years experience in drug R&D in large pharma and biotech firms.

Melissa Zafirelis

Director, Regulatory & Clinical Operations



Over 22 years multinational regulatory & clinical operations experience.

Igor Serov

Co-Founder & CFO



Over 20 years of investment banking experience

Brian Dawson

Senior Director, Process Development



25 years experience in development & commercialization of HbO₂'s products from pre-clinical research to product approval & marketing.

Arkadiy Pitman

Senior Director, Statistics & Data Management



20 years of pharmaceutical & healthcare US experience with strong background in mathematics, statistics & logistics.

Fantao Meng








Director of Research and Development



Hemoglobin specialist with 20 years of research experience in developing hemoglobin-based oxygen carriers (HBOCs)

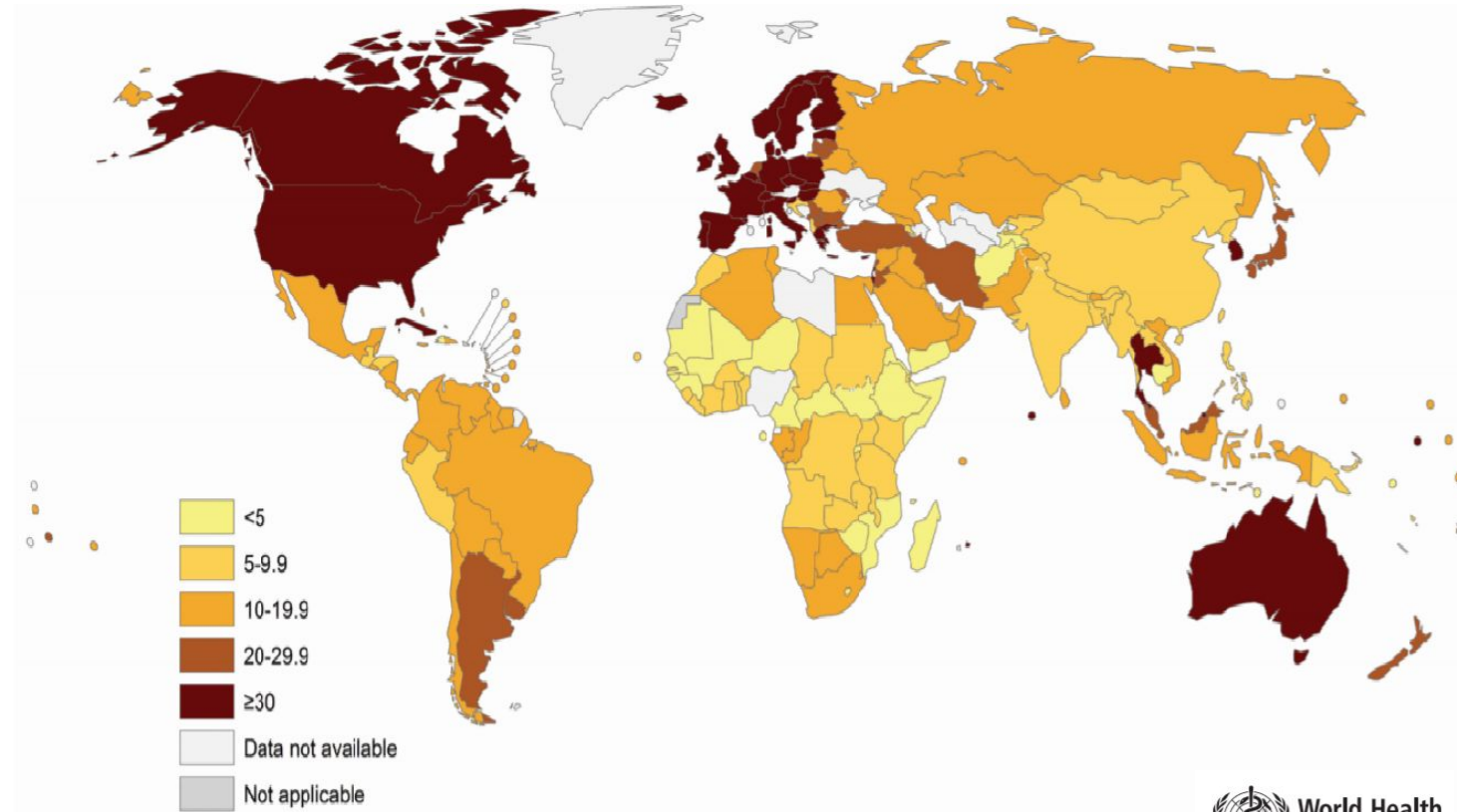
Hemopure and Oxyglobin

HBOCs with unique efficacy and safety profiles...

		Packed Red Blood Cells	Hemopure/Oxyglobin
	STORAGE	Refrigerated	Room temperature (2-30°)
	PREPARATION	Testing, typing, cross matching	Ready to use - no reconstitution
	COMPATIBILITY	Type specific	Universal
	SHELF-LIFE	42 days	36 months
	PURITY	Tested and screened for known infectious agents	Sterile pharmaceutical product
	RAW MATERIAL	Blood, limited availability	Bovine hemoglobine : abundant, controlled source
	EFFECTIVENESS	Dependant on storage length	Immediate oxygen delivery Same hemoglobin concentration as whole blood (13 g/dl)

Worldwide blood shortage

- Shortages of blood donations, not reaching the critical threshold of 30 per 1000 population in many countries
- COVID-19 pandemic highlights the need for a product that can successfully substitute blood's oxygen carrying capacity in time of need
- Hemopure has received marketing authorizations for acute anemia in South Africa & Russia



Global Status Report on Blood Safety and Availability 2016



**Russia and South Africa alone cumulate a 3 millions blood units shortfall.
Blood shortage represents a \$1 billion worldwide market per year.**

Prehospital Trauma & Medical Readiness



- Strategic National Stockpiles



- Out-of-hospital / Ambulance services



- Remote locations / Military battlefield use



Prehospital trauma (military & civilian) and disaster preparedness in the US markets represent \$500 million in revenue per year.

Blood Is Not An Option

- Blood disorders including Sickle Cell disease, Hemolytic Anemia, etc.
- Rare blood types
- Religious objectors (refuse blood transfusion).



160,000 patients with blood disorders need transfusions per year in US and Europe, which represents \$400 million in revenue per year. Religious objectors represent another \$149 million in annual revenue in the United States alone.



Blood shortage, a similar issue in veterinary markets

- 2 million canine transfusions are needed annually in US and in Europe
- Veterinary product is approved in US and EU
- 30 different species has been successfully treated with Oxyglobin
- Only up to 25% of veterinary transfusion blood supplies are covered by blood banks
- 84% of US veterinarians are dissatisfied with current options



The US and European canine markets represent \$550 million in revenue.



Organ Transplantation: Another Worldwide Shortage



- There is a constant demand for donated organs
- Organ eligibility criteria are extremely severe
- The ability to extend the life of organs ex-vivo and to assess their compatibility and health can dramatically improve the supply for transplantations
- The perfusion process allows doctors to assess reconditioning and viability of organs, limbs and tissues prior to transplantation both at room temperature and body temperature (37°C)

The transplantation market amounts to \$137 million per year.

➔ Additional indications include...

- Ischemia indications including
 - ✓ Minimization of infarct size (STEMI - ST-Elevation myocardial infarction)
 - ✓ Resuscitation from sudden cardiac arrest
 - ✓ Minimization of tissue loss in Limb ischemia / PAD claudication
- Antidote for carbon-monoxide and cyanide poisoning
- Oncology with solid tumors
- Burn victims and plastic surgery
- Perfusion of
 - ✓ Limbs prior to transplantation
 - ✓ Brain cells for diagnostic purposes

The average potential US market size in each of these new indications is \$500m.

Robust Pipeline

Product	Indication	Pre-Clinical	Proof of Concept	Pivotal	Approval	Marketing
Veterinary						
Oxyglobin	Anemia - Canine	✓	✓	✓	✓	✓
Oxyglobin	Anemia - Feline, Equine	✓	✓			Off-label use
Oxyglobin	Anemia - Zoological Species	✓	✓			Off-label use
Human						
Hemopure	Acute Anemia (S.Africa/Russia)	✓	✓	✓	✓	2022/23
Hemopure	Acute Anemia - Blood not an Option	✓	✓	✓	2023 EU/US	
Hemopure	Acute Anemia - Pre-hospital Trauma	✓	✓	on-going	2023/24	
ZK1	Organ Perfusion for Transplantation	✓	✓	✓	2022 EU	
ZK1	Limb / Flap Perfusion	✓	✓	2025		
HBOC-201	Smoke inhalation antidote	✓	✓	2022		
Hemopure	FDP reconstitution	✓	✓	2024/25		
HBOC-201	Solid tumor treatment	✓	2021			
HBOC-201	Ischemia	✓	✓	2026		

Strong value creating recent progress

- US Department of Defense signed and sponsored Hemopure trial for pre-hospital trauma
- Groningen liver transplantation trial finalized with 100% success
- Patent filed for HBOC/Freeze Dried Plasma combination
- Collaboration signed with Department of Defense and Teleflex on Hemopure use as a reconstitution agent for FDP
- Yale University brain perfusion study with Hemopure published in Nature
- Publication of high dose Hemopure case series
- Patent filed for smoke inhalation antidote
- Publication of an article supporting use of Hemopure in emergency preparedness including pandemics such as COVID-19

Strong value creating milestones

- FDA submission for Hemopure Phase 3 pivotal BNO clinical trial
- Start of hand transplant study
- Submission of the IDE for the kidney perfusion trial
- Oncology collaboration for the treatment of refractory solid tumors
- Completion of production facility
- Filing of CE Mark for perfusion solution
- cGMP facility validation by US & EU regulators
- Oxyglobin market launch
- Hemopure market launch in South Africa

Major academic & health centers collaborations



Expanded access program hospitals



Over 300 peer-reviewed publications

Pretransplant sequential hypo- and normothermic machine perfusion of suboptimal livers donated after circulatory death using a hemoglobin-based oxygen carrier perfusion solution

Yves de Vries¹, Aisling M. Maher², Maarten W. N. Nijsten³, Maurice J. M. Vermeij⁴, Aad P. van den Berg⁵, Mariëtte I. de Boer⁶, Carlotta Uda⁷, Maarten P. J. van't Hof-Grootenboer⁸, Otto B. van Leeuwen⁹, Peter Meyer¹⁰, Martin C. van't Hof-Grootenboer¹¹, Vincent F. de Maessenecker¹², Ruben J. Porte¹³

Therapie einer extremen Anämie mit vernetztem Rinderhämoglobin

Fallberichte mit Literaturübersicht

Restoration of brain circulation and cellular functions hours post-mortem

Parvathi Venkita¹, Rishan C. Fernando^{1,2}, Jeroen P. Jansz³, Terrence S. Pope^{1,2}, Ying M. Kwan^{1,2}, André M. P. F. de Sa^{1,2}, Felix P. Torres^{4,5,6}, Martin Dierkes^{1,2}, David Perkins^{1,2}, K. Sangeeta^{7,8}, Zhen W. Zhang⁹, Shreshth K. D. Divedi¹⁰, Albert J. Kwan⁹, D. Christian P. Lukersmith¹¹, Christian J. Weisner^{12,13}, David G. Baxter^{14,15,16,17,18,19}

Consult QD

Hemopure Saves the Life of a Patient With Severe Hemorrhage

Case highlights the utility of a blood substitute product when blood transfusions are not an option



Management of thymoma-associated pure red cell aplasia: A novel use of blood substitute HBOC-201 in a Jehovah's Witness

Maria M. Beldiarski¹, Cheryl Case², Scott T. Avolio³, Gregory P. Biale⁴, Gregory J. Kray⁵, Joel V. DeWitt⁶

Hemoglobin-Based Oxygen Carrier Rescues Double Transplant Patient From Life-Threatening Anemia

M. T. Cooper¹, O. Alami², D. Glandorf³, M. Lynn⁴

Addressing the unmet need of life-threatening anemia with hemoglobin-based oxygen carriers

Richard S. Woodruff¹, Amber G. Roberts², Ajay Maudeni³, Nicole H. Gannon⁴, Anthony M. Long⁵, Paul G. Vercel⁶, and Cary S. Silverman⁷

A case study of 10 patients administered HBOC-201 in high doses over a prolonged period: outcomes during severe anemia when transfusion is not an option

Marc Zimberg¹, Ted Griffin², Elizabeth J. Griffiths³, Gary Schwartz⁴, David S. Zander⁵, Jennifer Woodly⁶, Kim Hoon Han⁷, Amanda Vercel⁸, Michael Lynn⁹, and Joseph Kray¹⁰

Transplantation of High-risk Donor Livers After Ex Situ Resuscitation and Assessment Using Combined Hypo- and Normothermic Machine Perfusion: A Prospective Clinical Trial

Otto B. van Leeuwen¹, Eric², Yvonne de Vries³, Misato Fujiyoshi⁴, MD, PhD⁵, Maureen W. N. Nijsten⁶, MD, PhD⁷, Ryan Uhlirak⁸, MD⁹, Carl Van't Hof-Grootenboer¹⁰, Maureen J. M. Vermeij¹¹, Karen M. B. de Boer¹², Rogier van't Hof-Grootenboer¹³, Maureen J. de Boer¹⁴, Ruben J. de Boer¹⁵, Van't Hof-Grootenboer¹⁶, Vincent E. de Steyer¹⁷, and Ruben J. Porte¹⁸

Use of the blood substitute HBOC-201 in critically ill patients during stroke crisis: a three-case series

Jonathan M. Davis¹, Nura El-Haf², Nivah N. Shah³, Gary Schwartz⁴, Margarete Black⁵, James Walsh⁶, Clark Dubost⁷, and Robert Halton⁸

Journal of Cardiothoracic and Vascular Anesthesia

Journal homepage: www.jcvaa.com

A Bridge to Bloodless Surgery: Use of Hemoglobin-Based Oxygen Carrier for Anemia Treatment and Autologous Blood Preservation During Redo Pulmonic Valve Replacement

Henry Henderson, MD, Jonathan H. Chew, MD, Kenich A. Tanaka, MD, MSc

Use of a Hemoglobin Substitute (HBOC-201) to Treat Acute Anemia in a Leukemic Patient with Anti-Vel Antibodies

N. Teyssie Agnelli, MD, Kenneth Srinivasan, MD, Hamaa Hachimi, MD, Guillermo Mendivil, MD (ASCP), Kenneth K. Bass, MD, PhD, Yihong Jia, M.D., M.Sc., M.P.H., M. Fagan, MD, PhD

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The Use of an Acellular Oxygen Carrier in a Human Liver Model of Normothermic Machine Perfusion

Dobrota W. Leding, MD, PhD¹, Naveed H. Chohan, PhD², Loretta Wilson³, Van Dooren, MD⁴, Timothy D. Hall, PhD⁵, Daniel S. Glick, PhD⁶, Timothy D. Hall, PhD⁷, Timothy D. Hall, PhD⁸, Timothy D. Hall, PhD⁹, Timothy D. Hall, PhD¹⁰, Timothy D. Hall, PhD¹¹, Timothy D. Hall, PhD¹², Timothy D. Hall, PhD¹³, Timothy D. Hall, PhD¹⁴, Timothy D. Hall, PhD¹⁵, Timothy D. Hall, PhD¹⁶, Timothy D. Hall, PhD¹⁷, Timothy D. Hall, PhD¹⁸, Timothy D. Hall, PhD¹⁹, Timothy D. Hall, PhD²⁰

Hemoglobin glutamer 250 (bovine) in South Africa: consensus usage guidelines from clinician experts who have treated patients

Morgan Mac¹, Eric Hoogwerf², Lee White³, Barry Jacobson⁴, Emily Lyden⁵, Jacques Swinnen⁶, Martin A. Swanson⁷, Aisha Jansen⁸, Achraf van Gansbeke⁹, Nadia Algarni¹⁰, and Jonathan S. Jhu¹¹

BMJ Open Transplantation of high-risk donor livers after resuscitation and viability assessment using a combined protocol of oxygenated hypothermic, rewarming and normothermic machine perfusion: study protocol for a prospective, single-arm study (DHOPE-COR-NMP trial)

Bloodless reperfusion with the oxygen carrier HBOC-201 in acute myocardial infarction: a novel platform for cardioprotective probes delivery

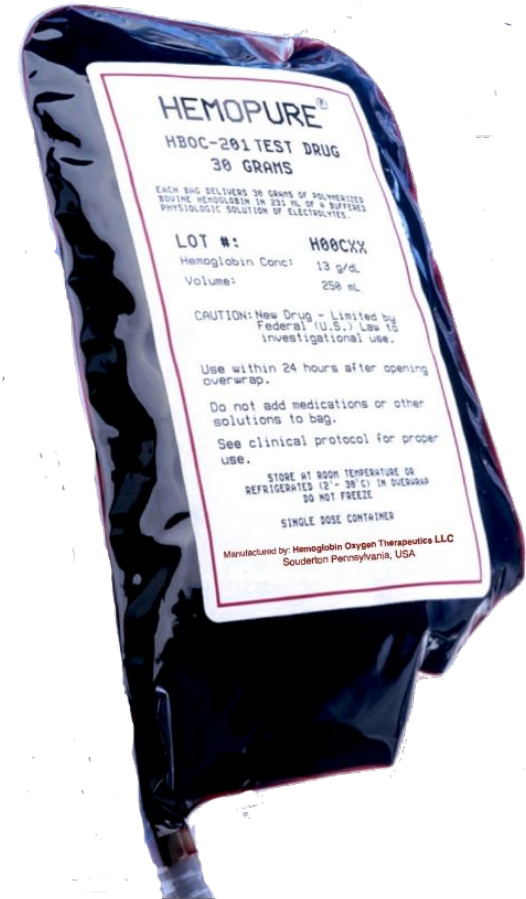
Jose M. Garcia-Ruiz¹, Carlos Colla-Vera², Rodrigo Fernandez-Juarez³, Javier Agudo⁴, Pedro Simón-González⁵, Ana García-Almer⁶, María Niño-Ayala⁷, Gregory P. Biale⁸, Rubén Zaldívar⁹, Gonzalo E. López-Morales¹⁰, Juan A. Torralba¹¹, Enrique Lora-Figueroa¹², Sergio Sánchez¹³

Abstracts

Abstracts from the 2017 meeting of the American Society for Blood and Hematology, held in Washington, DC, USA, from 14-18 November 2017.

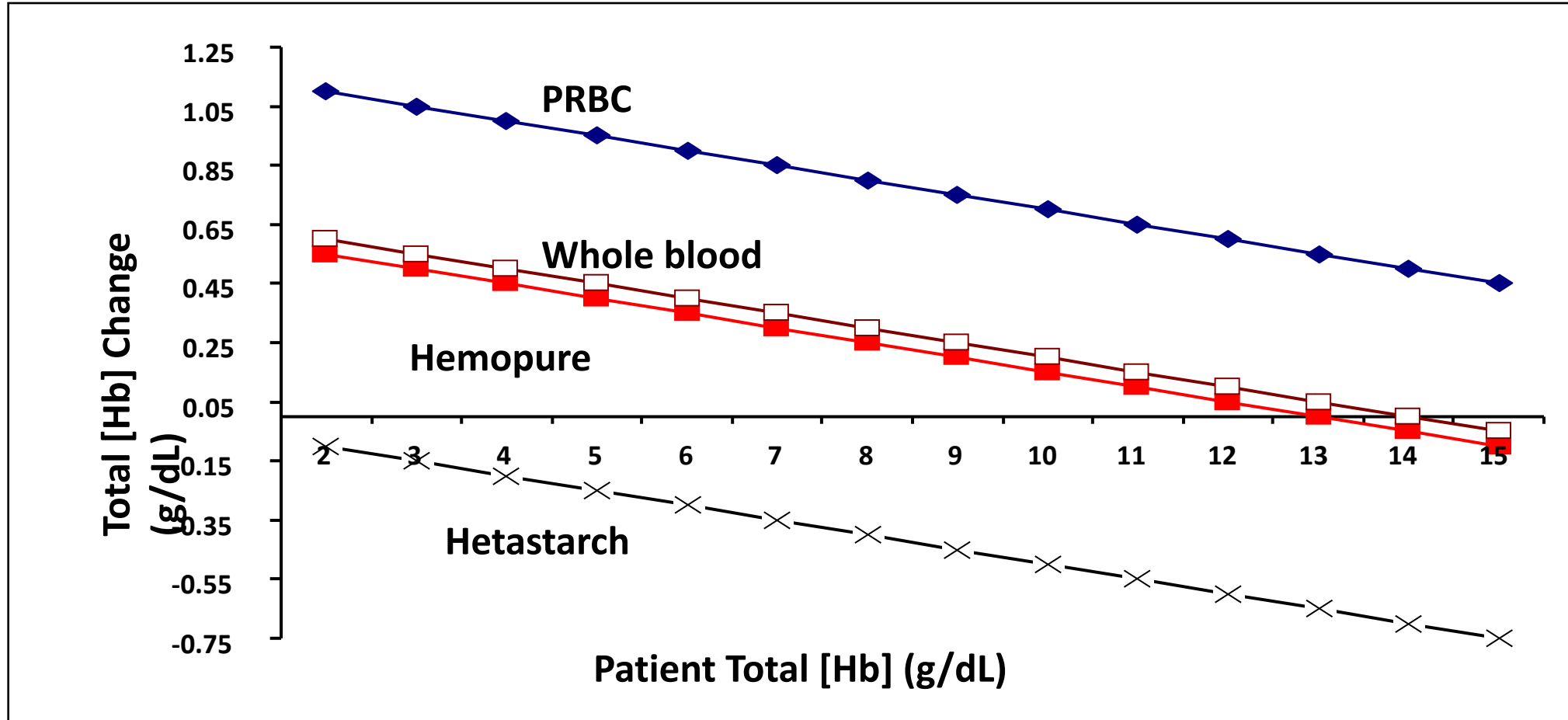
Characteristics of Hemopure

- Hb concentration 13 g/dL
- Plasma half-life ~ 19 hours
- Size = ~ 1 million < RBC
- Stable for 3 years at 2-30 °C
- Iso-osmotic, iso-oncotic
- P50 = 40 mm Hg
- Colloid (COP ~ to 6% albumin)
- Viscosity = 2.1 cP (~4 cP for RBC)



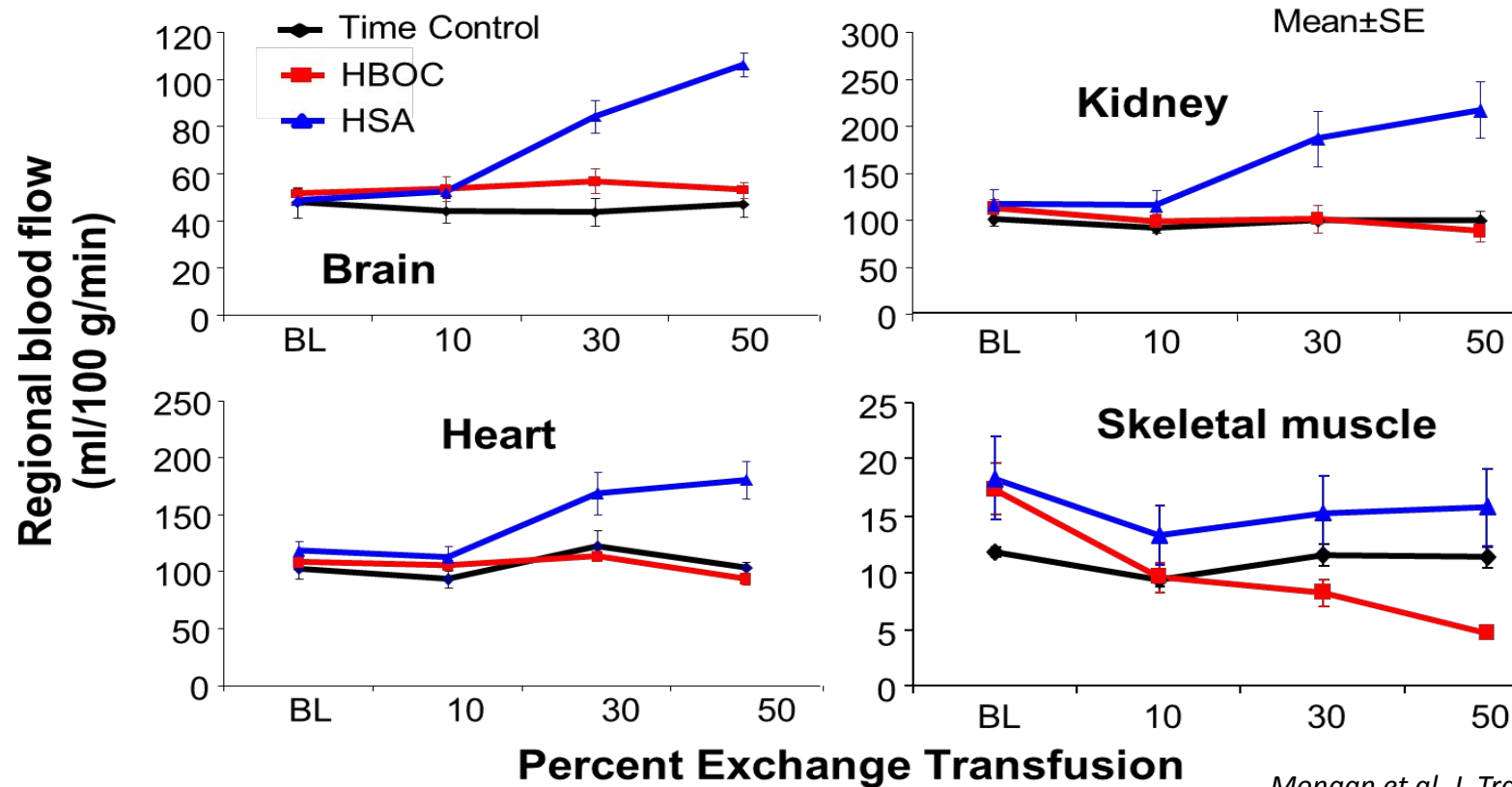
Relative Efficacy to Increase Total Hb

Impact of 250 mL : PRBCs > whole blood, > Hemopure, > hetastarch



Vital Organ Blood Flow

- MAP responds to Hemopure; \uparrow 10 – 20 mmHg
- Vital organ blood flow maintained



Mongan et al, J. Trauma 67:51-60, 2009

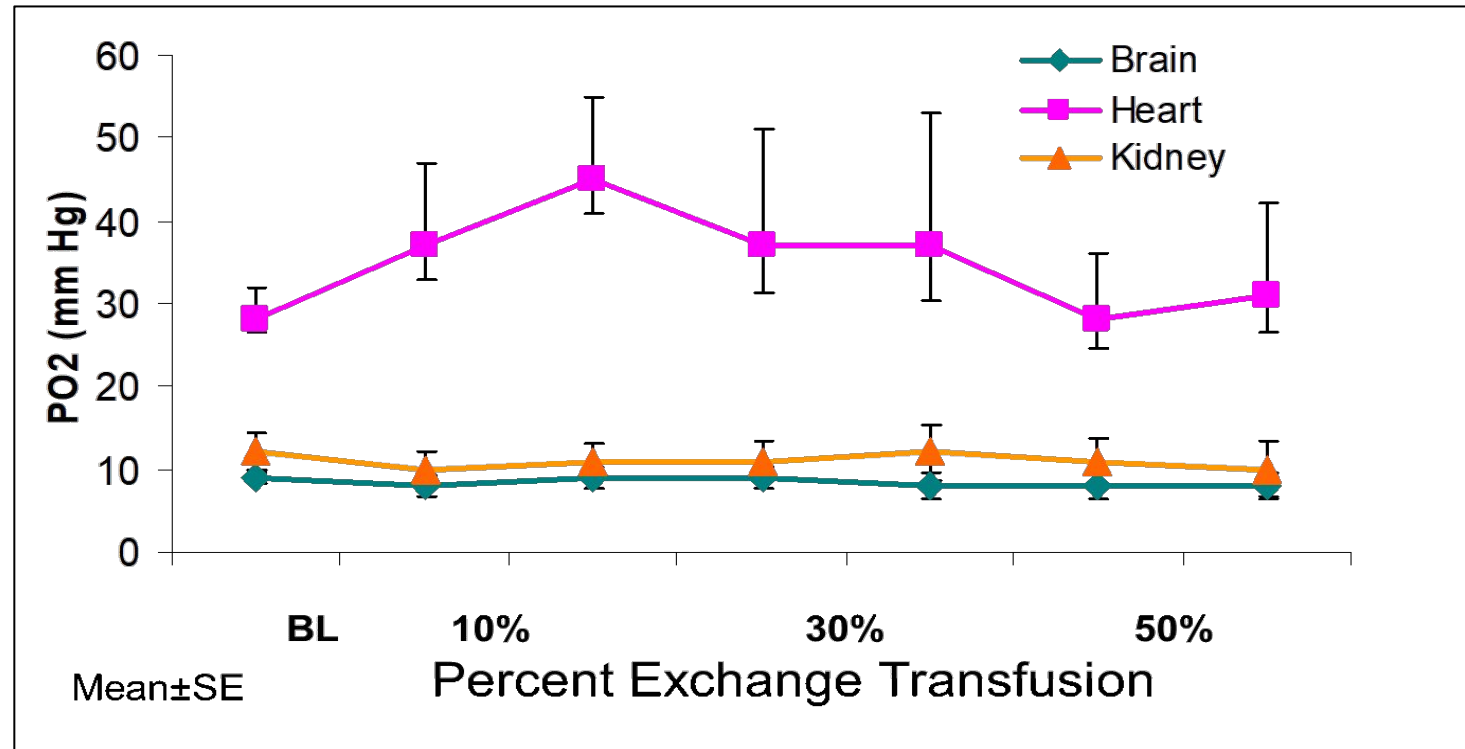
Tissue Oxygenation

Vital Organ Oxygenation Maintained

Model

- Hemodilution carried out in 3 stages: 10%, 30%, 50%
- Organ-specific tissue PO₂ determination via EPR imaging

Results



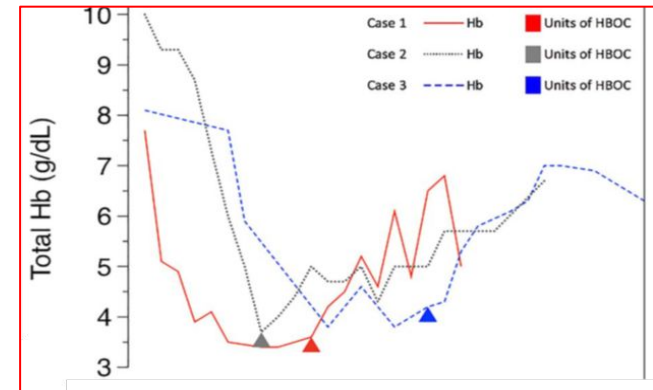
Muir et al Shock v35, 597-603, 2011

Expanded Access Real World Clinical Experience

Representative Cases

Three sickle cell patients in crisis: RBCs refused/unavailable

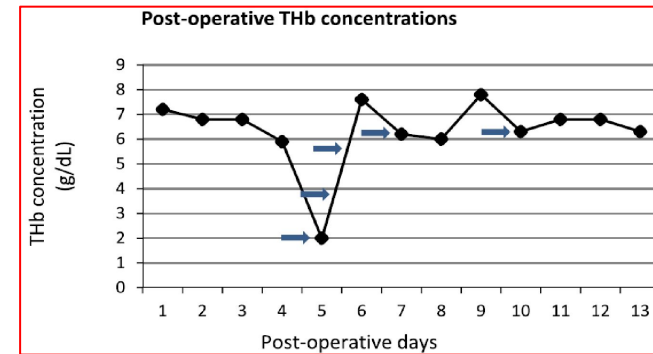
- Hb nadirs 3.5 - 4.0 g/dL
- Febrile, MOF, neurologic dysfunction.
- Hemopure administered: 6, 23, and 27 Units
- Full recoveries



Davis et al, Transfusion, v58, 132-137, 2017

Kidney – Pancreas transplant: RBCs refused

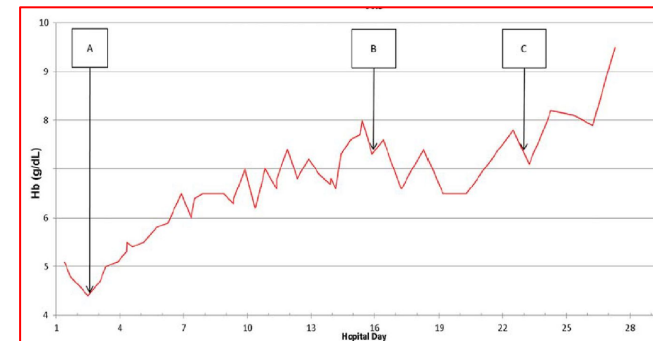
- Hb Nadir 2.0 g/dL
- Tachycardia, tachypnea.
- Hemopure administered: 12 units.
- Full recovery



Gomez et al, Am J Transplant, v17, 1941-1944, 2017

Autoimmune Hemolytic Anemia: RBCs refused

- Hb nadir 4.6 g/dL
- Elevated lactate
- Hemopure administered: 27 units.
- Full recovery



Epperla et al, Transfusion, v56, 1801-1806, 2016

Ex-situ Perfusion prior to Transplantation

Transplantation of high-risk donor livers after ex situ resuscitation and assessment using combined hypo- and normothermic machine perfusion: a prospective clinical trial

Declined livers (ECD = high-risk) 

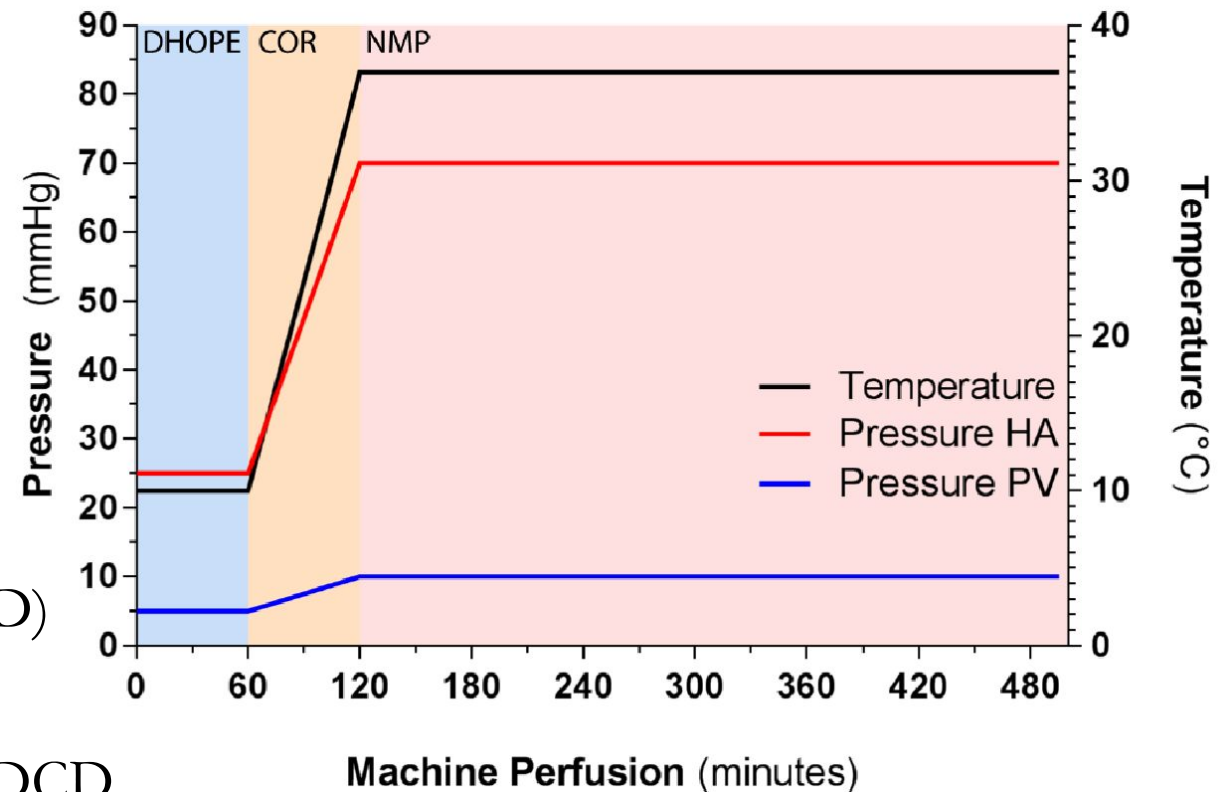
DHOPE = dual hypothermic oxygenated machine perfusion (4°C - 12°C).

COR = controlled oxygenated rewarming.

NMP = normothermic machine perfusion (37°C)

Post-operative results

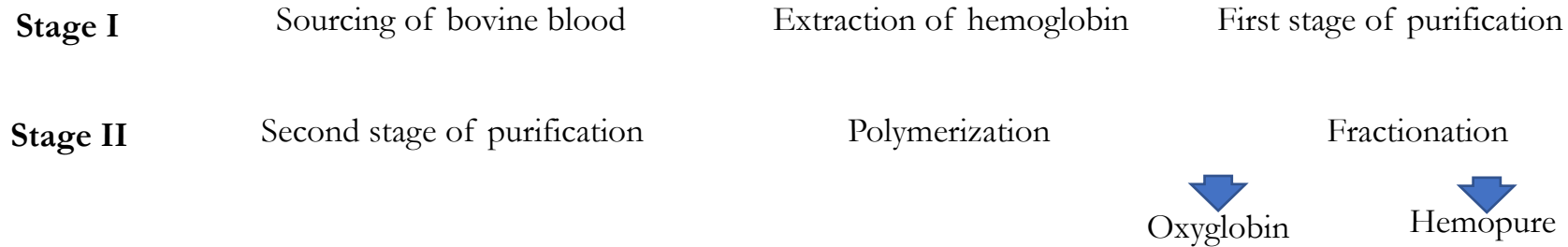
- 12-mo Graft survival: 100% (\geq std DCD & DBD)
- Peak ALT & AST: \ll std DBD & DCD
- DHOP-COR-NMP: \uparrow donor livers 20% vs. std DCD & DBD



Van Leeuwen et al, Ann Surg, 2019
de Vries Y, et al. BMJ Open 2019

Manufacturing capacities

The manufacturing process involves two stages:



- Facility building is fully constructed
- Stage I is in place and operational (\$20m replacement value)
- Stage II – all equipment is acquired and waiting for installation (\$70m replacement value)
- Production facility fully operational in 9 months
- Expansion capacity is secured on an adjacent plot



Certification from US and EU regulators is expected in 18 months

Cash positive in 2023 with \$50m investment

\$20m commitment secured

Year	2022 \$m	2023 \$m	2024 \$m	2025 \$m	2026 \$m	2027 \$m
Total Revenues	0.8	26.9	50.9	118.4	157.5	211
EBITDA	-16.6	8.9	29.1	93.4	125.3	168.9
Free Cash-Flow	-26.9	4.8	25.0	68.8	93.5	94.2

Why invest in HBO2 ?

Strengths

- Innovative products with superior competitive advantages
- Highly experienced team
- Existing approvals in both animal and human markets
- Distribution agreement for veterinary market
- Near term profitability and net cash flow

Opportunities

- Cash efficient plan to achieve market approvals and products launches
- Multi-billion dollar potential markets
- Potential additional indications
- Easy expansion into new geographical areas