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PEGylated Carboxyhemoglobin Bovine

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Disclosure

- Head of North American Clinical Operations
- No other financial relationships to disclose

Learner Objectives

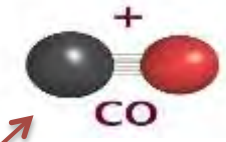
At the conclusion of this CME activity, the learner should be better able to:

1. Describe what is the investigational product PEGylated Carboxyhemoglobin Bovine
2. Discuss the mechanism of action of PEGylated Carboxyhemoglobin Bovine
3. Demonstrate narratively the potential use of PEGylated Carboxyhemoglobin Bovine in patients with Sickle Cell Disease

PEGylated Carboxyhemoglobin Bovine

- PEGylated Carboxyhemoglobin Bovine is an investigational IV therapeutic designed to treat either systemic or localized hypoxia caused by an ischemic or anemic event

PEGylated Carboxyhemoglobin Bovine: What is it?



Hemoglobin Molecule

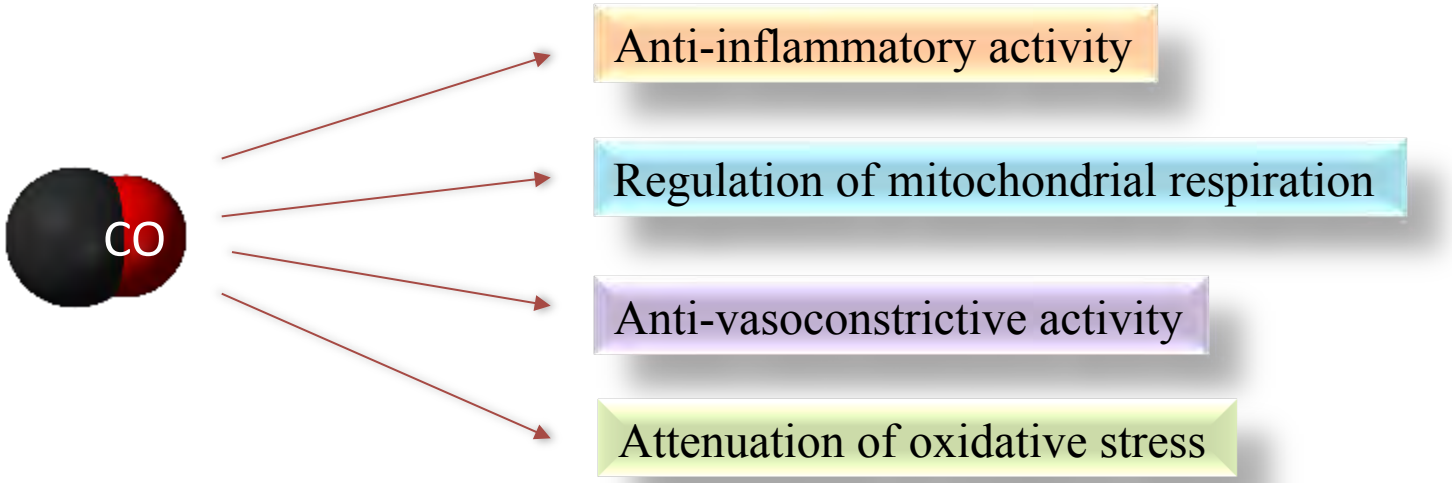
Polyethylene glycol (PEG)

PEGylated Carboxyhemoglobin Bovine

- **Orphan Drug designation** for treating the "comorbidities" of sickle cell disease
- **5 INDs** and over 47 eINDs approved by FDA
- **250+ subjects exposed** to more than 650 infusions (as many as 17 in one patient)
- No evidence of serious adverse drug reactions in severely anemic patients

PEGylated Carboxyhemoglobin Bovine MOA: Carbon Monoxide (CO)

- Following infusion, PEGylated Carboxyhemoglobin Bovine is designed to rapidly release a low level of therapeutic CO
- CO is a well recognized endogenous mediator



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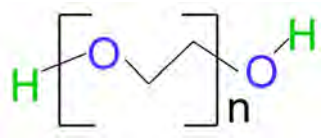
Song, B et al. *Presented at Experimental Biology.* 2016; Zhang J et al. *J Appl Physiol.* 2012; Klaus AJ, et al. *Artif Cell, Blood Subst Biotech.* 2010; Ananthakrishnan R, et al. *Artif Cells Nanomed Biotech.* 2013.

PEGylated Carboxyhemoglobin Bovine MOA: Polyethylene Glycol (PEG)

- PEGylation confers beneficial characteristics to therapeutic proteins



- Increased circulating life
- Decreased immunogenicity
- Rheological properties
- Inhibition of extravasation

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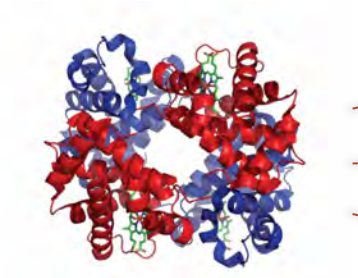
Pasut G et al. *Prog Polym Sci.* 2011; *Dongxia Li et al. Biochim Biophys Acta.* 2008.

PEGylated Carboxyhemoglobin Bovine MOA: Bovine Hemoglobin

- Highly effective gas carrying and transfer protein

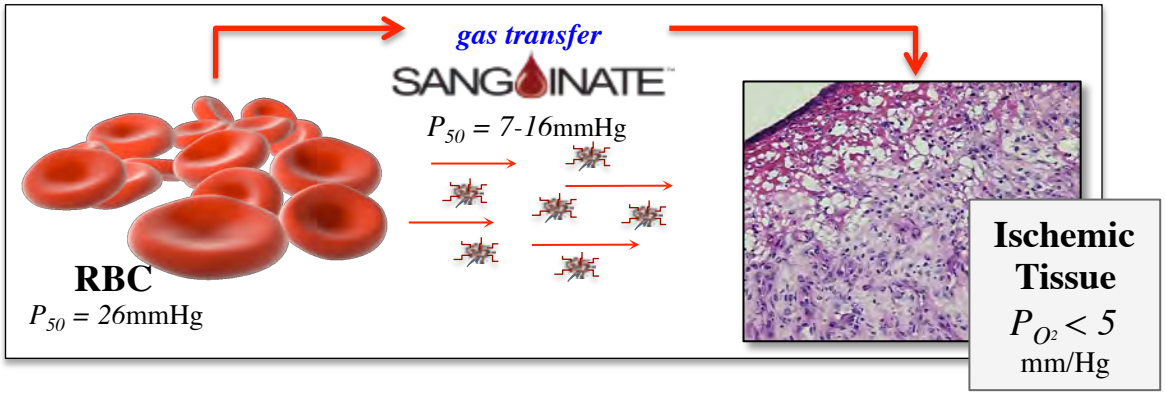


Optimal gas transfer kinetics

Well Controlled source material

Abundant product supply

PEGylated Carboxyhemoglobin Bovine O_2 *Transfer* Mechanism



P_{50} is key to PEGylated Carboxyhemoglobin Bovine's oxygen transfer properties in delivering oxygen to hypoxic tissue

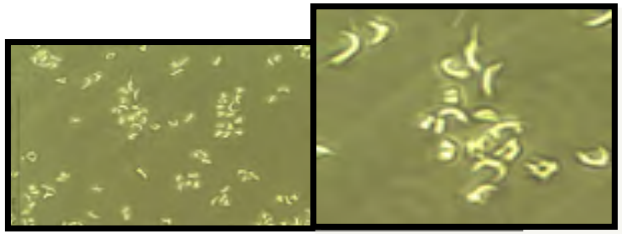
- P_{50} is between the P_{50} of RBCs and low P_{O2} of ischemic tissue
- *Designed to* transport oxygen from RBC to essential sites with hypoxia

MOA is unique compared to any previously developed biologic

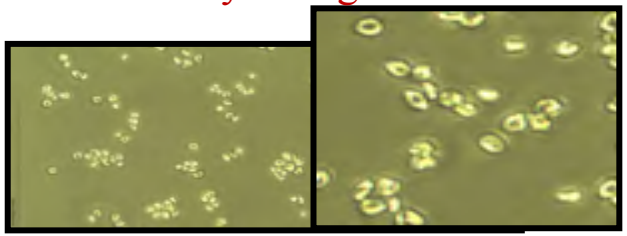
PEGylated Carboxyhemoglobin Bovine: Proof of Oxygen Transfer

PEGylated Carboxyhemoglobin Bovine transfers oxygen and restores morphology to Sickle Cells *in vitro*

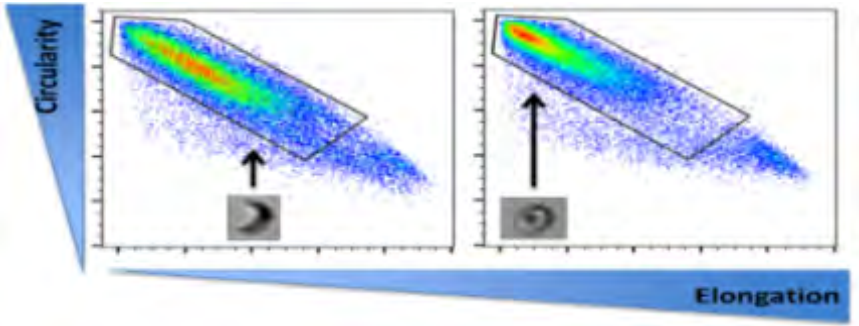
Control



Post PEGylated Carboxyhemoglobin Bovine



Imaging Flow Cytometry: Quantitative



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Jubin R, et al. *Presented at ASH.* 2014.

Phase Ib Clinical Trial – Non-crisis SCD Patients

- Open label, 24 participants, randomized 2:1 ratio
- Single 2-hour IV infusion of either 160 mg/kg or 320 mg/kg of PEGylated Carboxyhemoglobin Bovine
- **Primary endpoint:** the safety of PEGylated Carboxyhemoglobin Bovine vs. hydroxyurea
- **Secondary endpoints:** determination of the plasma pharmacokinetics and assessment of hematologic measurements
- No evidence of a clinically meaningful safety concerns were identified
- Study Sites: 2 countries and four medical centers in Central and South America

Misra H., et al. *Rev Bras Hematol Hemoter.* 2017;39(1):20–27.

Current Clinical Development Programs in SCD

- Phase II VOC A. Ambulatory setting – recruiting patients
- Phase II VOC B. Hospital setting – recruiting patients
- Phase II SCD leg ulcer study – enrollment complete

ClinicalTrials.gov

Study of PEGylated Carboxyhemoglobin Bovine in the Treatment of Sickle Cell Disease Patients with Vaso-Occlusive Crisis

This study is currently recruiting participants. (see Contacts and Locations)

Verified November 2016 by Prolong Pharmaceuticals

ClinicalTrials.gov Identifier: NCT02411708

Purpose

Safety and effect of PEGylated Carboxyhemoglobin Bovine on Sickle Cell Disease patients experiencing a vaso-occlusive crisis

- Phase II, randomized (2:1) ratio, placebo-controlled, single dose, single-blind study in ambulatory settings (ie. infusion clinics, ED)
- 2-hour IV Infusion
- Estimated enrollment: 24 adult participants
- **Primary Outcome Measures:** Time to readiness for discharge from ambulatory site
- **Secondary Exploratory Observations:** Blood Morphology, Markers of inflammation and adhesion
- Blood samples are being collected (prior to infusion, at time of discharge and 72-hours post discharge) to assess the impact of PEGylated Carboxyhemoglobin Bovine on RBC morphology and inflammatory markers

ClinicalTrials.gov

A Study of PEGylated Carboxyhemoglobin Bovine for the Treatment of Vaso-Occlusive Crisis (VOC) in Adult Sickle Cell Disease Patients)

This study is currently recruiting participants. (see Contacts and Locations)

Verified March 2017 by Prolong Pharmaceuticals

ClinicalTrials.gov Identifier: NCT02672540

Purpose

Safety and effect of PEGylated Carboxyhemoglobin Bovine on Sickle Cell Disease patients experiencing a Vaso-Occlusive Crisis who are admitted to the hospital for treatment.

- Phase II, multicenter, randomized (2:1) ratio, placebo-controlled, single-blind study in hospital settings
- 2-hour IV Infusion
- Estimated enrollment: 30 adult participants
- **Primary Outcome Measures:** Time to readiness for discharge from the hospital
- **Secondary Outcome Measures:** Safety of treatment, proportion of patients who develop ACS, who are re-hospitalized, total length of stay, reduction in total pain medication, reduction in pain score, reduction in level of C-reactive protein
- Study Sites: Colombia, Dominican Republic, Honduras, Panama

ClinicalTrials.gov

PEGylated Carboxyhemoglobin Bovine in Sickle Cell Disease Associate Leg Ulcer (LU)

This study has been completed.

ClinicalTrials.gov Identifier:
NCT02600390

Purpose

PEGylated Carboxyhemoglobin Bovine Sickle Cell Disease associated Leg Ulcers

- Phase II, Open Label, repeated-dose, dose escalation study
- 2-hour IV Infusion once a week over a 4-week or 6-week period
- Estimated enrollment: 10 adult participants
- **Primary Outcome Measures:** Safety of treatment, change in SCD leg ulcer wound pain measured with a pain scale, rate and extent of leg ulcer wound healing as measured by change in wound surface area.
- **Secondary Outcome Measures:** Changes in leg ulcer status as measured by need for debridement, extent of exudate production, type an amount of granulation tissue, wound and skin appearance, changes in quality of life
- Study Sites: Dominican Republic, Panama

To-Date SCD Patients Treated with PEGylated Carboxyhemoglobin Bovine

Sickle Cell Disease (SCD) – *Sickle Cell Specific*	**Number Treated**
Stable SCD (Phase I)	24
Leg Ulcer (Phase II)	10
Vaso-Occlusive Crisis (Phase II; In-hospital study)	20
Vaso-Occlusive Crisis (Phase II; Ambulatory study)	10
Emergency IND	
Vaso-Occlusive Crisis + Hemolysis	3
Acute Chest Syndrome	2
Bone Marrow Transplantation	1
Phase I Study (acute severe anemia when blood is not an option)	
Acute Chest Syndrome	3
Hyper-Hemolysis	1
Gastro-Intestinal Bleed	1
Total	75

SCDTrialMap.com

- Site designed to ease locating clinical trials
- Launched at SCDAA Convention September 30th, 2016
- Goal to have link posted on regional and national CBO websites

http://scdtrialmap.com/

Future Clinical Plans in SCD

- Pivotal efficacy trial in planning stage for ambulatory setting
- Other SCD comorbidities under consideration:
  - Stuttering priapism
  - Acute chest syndrome
  - Hyper-hemolysis
  - Splenic sequestration

Thank You