Bio-inspired design approaches to artificial blood technology: Oxygen carriers

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Allan Doctor, MD, Professor of Pediatrics at the University of Maryland School of Medicine, shares his expertise on bio-inspired design approaches to artificial blood technology: oxygen carriers

Statement of need

There is a need for an artificial oxygen (O_2) carrier for use when banked blood is unavailable or undesirable.

To date, efforts to develop Hb-based oxygen carriers (HBOCs) have failed successful translation, because of design flaws that do not preserve physiologic interactions of normal red blood cells (RBCs): First, HBOCs capture O_2 in lungs but do not release O_2 effectively to tissue, and second, HBOCs trap nitric oxide (NO), causing vasoconstriction – which critically limits blood flow, particularly in ischemic vascular beds; together, failure to both effectively release (to tissue) captured O_2 and blood flow restriction undermines the potential benefit from otherwise improved O_2 content.

Bio-inspired design principles

Broadly speaking, existing and near-future technologies that rely on standard design and manufacturing techniques may be insufficient to address urgent challenges, including those to our natural environment (climate change, pollution), our built environment (failing infrastructure, integrated manufacturing), and our health (aging populations, food scarcity, vaccine development).

Bio-inspired design – concepts, approaches, and technologies that build and control the way nature does – offers transformative solutions to these problems. Bio-inspired technologies share function and/or structure with nature.

The above approach has recently been applied to developing biosynthetic analogues to ‘natural’ blood components. Enabled by transformative advances in the areas of synthetic chemistry, biomaterials and nano-fabrication, an exciting area of research has emerged with a focus on development and evaluation of semi-synthetic or synthetic ‘bio-inspired’ surrogates of blood products that can be manufactured at large scale (i.e. sufficient availability), can be sterilized without compromising biofunction, and stored as small volume deliverables over long periods of time across broad ambient temperature ranges and

environmental conditions (i.e. easy storage and portability), can be easily reconstituted and administered ‘on demand’ in far forward scenarios (i.e. pre-hospital applicability), can potentially avoid the need for type matching (universal application with minimal immunogenic risk), can circulate safely upon intravascular administration without systemic risks, and can mimic, leverage and amplify endogenous mechanisms of blood component function to mitigate the effects of traumatic exsanguinating hemorrhage.

This field of research has developed in the areas of functionally mimicking blood’s cellular as well as non-cellular components. It continues to focus on resolving translational challenges concerning biocompatibility, safety, pre-hospital availability, and universal applicability.

Key features of RBC physiology for design emulation

Modulation of O_2 Affinity

In brief, O_2 capture in the lung is achieved by strong natural affinity of hemoglobin (Hb) for its ligand, O_2. The effective release of O_2 to respiring cells however, is facilitated by a complex, context-responsive process in RBCs that reduces Hb~O_2 affinity in direct proportion to biochemical cues of perfusion insufficiency (acidosis and hypercapnia improve O_2 release, as does RBC ‘metabolic memory’ which controls the concentration of 2,3-DPG – a molecule that also improves O_2 release from Hb); this physiology is reversed during subsequent transit through the lung, renewing high Hb~O_2 affinity and robust O_2 capture.

Modulation of regional blood flow

Microcirculatory blood flow is regulated to instantaneously match O_2 delivery to dynamic variation in metabolic demand. This extraordinarily sensitive programmed response to tissue hypo-perfusion is based upon context-responsive control of vasoactive effector bioavailability (such as NO, among others) by RBCs in a fashion that directly couples vascular tone (and blood flow) to O_2 availability in the lung and to O_2 consumption in the periphery (RBCs either sequester or export NO, as they traverse ascending or descending O_2 gradients, respectively).

In normal RBCs, NO capture/release is modulated by O_2 responsive membrane properties, enzyme and transport systems, cell morphology, and rheology.

Bio-Inspired approaches to oxygen carriers

We have employed a formal bio-inspired design to develop and optimize ErythroMer (EM, currently under development by KaloCyte, Inc.) to emulate the key RBC physiologic features (above) that stabilize O_2 transport under severe physiologic stress. EM has been designed with five significant innovations, including unique shape, morphology, and biocompatibility, resembling RBCs.

EM is a first-in-class, bio-synthetic nanocyte that modulates O_2 affinity to context during circulation (lungs ↔ tissue), slows NO trapping while permitting O_2 diffusion, recycles oxidized Hb via simple reduction, and allows lyophilization, facile reconstitution, and extended shelf life. EM is a self-assembled, deformable, peptidic-lipid amphiphile-based nanoparticle incorporating a high hemoglobin (Hb) payload.

The EM shell is composed of an amphiphilic precursor with pH-responsive peptidic groups that serve as 'wetware' by linking binding availability of the natural allosteric effector 2,3-DPG to the same biochemical cues of perfusion sufficiency that modulates Hb O_2 affinity (through other means). This design recapitulates context-responsive control of O_2 binding in RBCs.

Also, the construct's phosphatidylcholine 'head' group facilitates biocompatibility of the exofacial surface, mimicking endogenous biomolecules, and is subject to enzymatic digestion and degradation in vivo to end-products identical to that of 'natural' amino acids, lipids, and endogenous biomolecules.

The EM lead prototype has passed rigorous initial ex vivo and in vivo "proof of concept" testing, which indicates this design surmounts prior challenges in emulating normal RBC physiologic interactions with O2 and NO. In multiple, multi-species models of major bleeding/anemia, EM reconstitutes normal hemodynamics and O_2 delivery, observed at the system, tissue, and cellular level. Moreover, EM potential for extended ambient dry storage and immediate, simple reconstitution has significant implications for portability and use. The next steps include formulation scaling, a detailed study of pharmacokinetics, biodistribution, and safety, and evaluation in large animal models of hemorrhagic shock.

Summary

In pre-hospital, austere military, and other resource-limited settings where stored blood products are frequently unavailable, undesirable, or in short supply, there is a critical need for a transportable, temperature-stable blood substitute containing an artificial oxygen (O_2) carrier, to treat life-threatening bleeding with a product that closely emulates the performance of RBCs during severe physiologic stress.

To address this need, we have developed ErythroMer (EM), a first-in-class, bio-synthetic hybrid lipid-polymeric nanoparticle that incorporates high per particle payloads of hemoglobin (Hb) as well as a sophisticated physiologic control system encoded as 'wetware' in the nanoparticle shell. As such, the EM bio-inspired design has yielded a prototype that = emulates key RBC physiology and represents a potentially disruptive introduction into Transfusion Medicine.

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