Recent advancements in artificial blood technology

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Professor Allan Doctor from the University of Maryland School of Medicine shares promising developments regarding the creation of safe and effective artificial blood products

Haemorrhage accounts for approximately 35% of civilian and approximately 90% of military potentially survivable in-field deaths.

However, logistic challenges (blood typing, donor availability and cold chain) limit blood deployment in resource-limited and austere environments. As such, a ‘universal donor’, shelf-stable, portable whole blood analogue (WBA) could transform care in both civilian and military settings.

Multiple research programmes have been striving to enable field resuscitation with a fluid that would perform similarly to ‘natural’ whole blood (restore blood pressure, O2 delivery, and haemostasis – the ability to form blood clots). Viable prototypes have been developed separately for each blood component and are ripe for integration to create artificial blood.

First-generation blood substitutes and artificial blood

Oxygen (O2) carriers ‘first-gen’ designs comprised two approaches: perfluorocarbon emulsions and simple polymerised haemoglobin (Hb, PolyHb). Both failed to emulate normal red blood cell (RBC) physiology because of design flaws which did not preserve physiologic interactions with O2 – to capture O2 in the lungs and release O2 effectively to tissue – and with nitric oxide (NO) to support (rather than interfere with) NO based regulation of blood vessel caliber, which caused vasoconstriction.

We now appreciate that a major problem with the ‘first gen’ designs is the significant abundance of low molecular weight (LMW) PolyHb species which elicit vasoconstriction, hypertension, and oxidative injury and were associated with death, heart attack, and stroke, prompting premature FDA closure of their phase 3 trials. In a novel approach, a US team (Palmer Lab, Ohio State University, in preclinical development) optimised the PolyHb MW profile, limiting adverse effects and modulating O2 affinity to emulate RBCs more closely.

Other promising ‘next-gen’ approaches encapsulate Hb in nano-assembled membranes to create bio-synthetic artificial cells: haemoglobin vesicles (HbV, Sakai Group in Japan, now in phase 1 human trials) and (ErythroMer, EM, developed in the US by KaloCyte and University of Maryland, in final pre-clinical development) are first-in-class, bio-synthetic, nano-cytes that closely imitate RBC physiology.

EM modulates O2 affinity to context during circulation, slows NO trapping while permitting O2 diffusion, recycles oxidised Hb via simple reduction and (EM, but not HbV) allows lyophilisation with facile reconstitution, permitting extended shelf life under temperature extremes and enabling field deployment.

Producing safe and effective dried plasma

First developed in the 1930s, freeze-dried plasma was widely used by British and American forces in WWII and the Korean War but was abandoned because of disease transmission risk. Modern methods to improve blood safety have made it possible to produce safe and effective dried plasma, now available in France, Germany, South Africa, and a limited number of other countries. Octapharma commercialised a solvent/detergent (S/D) treated pooled plasma, producing a frozen product that has since been administered safely to millions of patients.

Other available dried plasmas include French Lyophilised Plasma (FLYP), produced by the French Military Blood Institute (Centre de Transfusion Sanguine des Armees [CTSA]), LyoPlas N-w, produced by the German Red Cross and Bioplasma FDP, produced by National Bioproducts Institute, Pinetown, South Africa.

Additional promising products are in advanced development employing different drying methods, pathogen reduction, pooling, packaging, and other approaches. Two promising products are EZPLAZ, in development by Teleflex (FDA approval in process) and FrontlineODP (Velico Medical), a spray drying unit that can generate dry plasma. Velico's device is in phase 2 human clinical trials; a 510k device approval for commercial availability is anticipated for Q1 2025, enabling blood banks to produce SDP locally.

The University of Maryland is exploring the formulation of a modular, adaptive plasma analogue (MAPA) based on a novel polymerised Albumin construct (polyAlb, Palmer Lab, Ohio State University) and select freeze-dried human clotting factor concentrates. MAPA composition would be customisable to context/need (e.g., for simple volume expansion or to promote hemostasis), and polyAlb may be used for simple haemorrhage alone. In the setting of trauma-induced coagulopathy (TIC), (currently approved) coagulation factor concentrates (fibrinogen and prothrombin complex concentrates) and haemostatic pharmaceuticals (tranexamic acid) would be co-administered.

Platelet technologies

Currently, two promising approaches are underway to enable field deployment of platelets in resource-limited settings. The first is Thrombosomes developed by CellPhire which is in human phase 2 trials. Throbosomes are a natural platelet-derived haemostatic technology comprising freeze-dried platelet-derived membrane vesicles that limit bleeding in models of trauma and thrombocytopenia.

Alternatively, SynthoPlate (SP, in advanced preclinical development by Haima Therapeutics and Case Western Reserve University) is a biocompatible liposomal nanoparticle-templated 'platelet surrogate' technology with surface presentation of

synthetic peptides to mimic ‘natural’ platelet injury site-selective adhesion and aggregation. Freeze-dried SP has demonstrated haemostatic efficacy and survival benefit in traumatic haemorrhage models and is storage-stable at a wide range of ambient storage conditions. Notably, the identity and density of SP surface ligands are customisable, enabling precise performance adaptation to context.

Integrating components into a field-deployable whole-blood analogue

The US Department of Defense Advanced Research Projects Agency delivery (DARPA) recently established a four-year programme to develop, evaluate, and rapidly translate a first-in-class formulation and delivery system for a field-deployable whole blood analogue (WBA). The University of Maryland, Baltimore (UMB) Center for Blood Oxygen Transport & Hemostasis (CBOTH) and Center for Translational Medicine (CTM) were selected to lead this effort to optimise and integrate a comprehensive set of WBA prototypes into an artificial blood solution that matches performance to ‘natural’ whole blood.

The prototype portfolio for this effort includes multiple lead haemoglobin-based O2 carrier component candidates (PolyHb and ErythroMer), both pathogen-inactivated freeze-dried plasma (EZPLAZ FDP) and, potentially, a condition-specific, modular adaptive plasma analogue (MAPA), as well as nanoparticle platelet mimetics (SP). This effort includes an artificial intelligence (AI) based system to guide blending combination, improvement, and down-selection of WBA components. DARPA programme objectives also address the need for production efficiency and scaling, effective technology transfer, regulatory approvals, clinical trials, licensing, and commercialisation.

Overall, artificial blood research programmes are advancing rapidly, with individual/combined prototypes ready or approaching readiness for technology translation and commercialisation in the near future.

Please Note: This is a Commercial Profile