Horizon Scan of the Artificial Blood Research and Funding Landscape

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Key findings

- Eleven clinical trials were identified relating to artificial blood products. Of these, the trial status for five was terminated or unknown, three were recruiting or not yet recruiting and three completed. No study results were published.
- Four trials were sponsored by industry and seven by other sponsors, such as universities, healthcare organisations and individual researchers.
- The highest number of trials was carried out in France and the USA (three each), followed by the UK and Hong Kong (two), then New Zealand (one).
- Six technologies were identified across these trials with HEMO2life being the most investigated (four trials)
- Our funding scan identified nine non-NIHR projects worldwide, with the majority being in the UK. The largest proportion of total funding spend (£2.1 million) was from the Wellcome Trust across two projects. However, most projects (five) were funded by the National Institute of Health (NIH) in the USA.
- In the published literature, including preclinical studies, haemoglobin-based oxygen carriers were most prevalent, with most research happening in the USA, China, Europe, Canada, and Japan. Two technologies (PolyHb and VS-101) are in preclinical studies only; five other technologies (HemAssist, PolyHeme, Hemolink, Hemospan, and Hemoximer) have been discontinued.

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Horizon Scan of the Artificial Blood Research and Funding Landscape

Current literature

Locations performing the most research in this field:

- USA
- China
- Europe
- Canada
- Japan

Haemoglobin-based oxygen carriers were the most investigated

Some technologies:

- Are only in pre-clinical studies
- Have been discontinued

Trial data

11 clinical trials worldwide

Study Locations

3 France | 3 USA | 2 UK | 2 Hong Kong | 1 New Zealand

4/11 trials for HEMO2life®

6 different technologies identified

No results currently available

5 trial status unknown/terminated

3 recruiting/not yet recruiting

3 Completed

Funding

£2.1M from the Wellcome Trust across 2 projects

9 Non-NIHR projects worldwide (most in the UK)

45.5% National Institute of Health (NIH) provided 45.5% of project funding, making it the top funder.

Background

What is artificial blood and how is it used?

We have focused on artificial blood or blood products used to support transport of oxygen around the body. We have not considered other methods used to support blood volume only.

There are two major types of oxygen therapeutics: haemoglobin (Hb)-based oxygen carriers (HBOCs) and perfluorocarbon-based oxygen carriers.[1] The Hb for most HBOC products is derived from expired human blood, fresh bovine (cow) or porcine (pig) blood, and some marine invertebrates. The production of HBOCs involves the chemical modification of harvested Hb using methods including polymerization (creating Hb chains), cross-linking Hb tetramers (Hb molecules consist of four sub-units in total (two α-subunits and two β -subunits) – meaning they are tetramers) or encapsulating Hb within membranes that mimic the environment present within red blood cells (RBCs). These methods are used to reduce toxicity that can lead to adverse effects in artificial blood recipients and prolong the half-life of the Hb.[2]

Methods

Literature searches

Searches for trial records were conducted on the Clinicaltrials.gov trial registry and the Innovation Observatory's ScanMedicine trial portal on 24th April 2024, using a range of terminology relating to artificial blood either generally or for specific products. Searches for funding data were conducted on a range of funding platforms (see appendix for details). A targeted search for reviews plus a more specific and limited search of non-review articles was conducted on Ovid Embase. A date limit of 2019 onwards was applied across all searches (trial completion date, funding end date, review/article publication date). See appendix for full details of all searches.

Eligibility criterion

The eligibility criterion was any product that aimed to perform a key function of blood, namely the transportation of oxygen around the body.

Record selection

Bibliographic records were screened using Rayyan software. Clinical trials and funding data were screened in situ, with screening decisions recorded on an Excel spreadsheet. Due to the rapid nature of this project, one person (LT, AS, RP, or ER) screened each record.

Data extraction and quality assessment

Data were extracted and synthesised by one person (LT, RP or ER) per section (funding data, clinical trials and published evidence). Quality assessment of records was not undertaken as the scope of this project was to identify products, technologies, funding and companies as opposed to assessing the methodological quality of the evidence on this topic. The report was edited and finalised by GN.

Innovation Landscape

Clinical trials

From 2019 onwards, there were 11 clinical trials[3-13] that satisfied the inclusion criterion, covering the following artificial blood products:

- HBOC-201 (Hemopure)[14]
- Whole blood analog (unnamed)
- Marine oxygen carrier M101 (HEMO2life)[15]
- Perfluorocarbon ABL-101[16]
- PP-007 (Sanguinate)[17]
- YQ23[18]

Of the 11 trials, France and the USA hosted the most (n=3), followed by Hong Kong and the UK (n=2), then New Zealand (n=1). This seems to follow the locations where artificial blood products are developed and manufactured: HemO2life is developed by the French company Hemarina,[15] HemoPure by the USA company HbO2 Therapeutics,[14] and YQ23 by the Hong Kong company New Beta Innovation[18]. Two companies were also identified independently from the clinical trials search; NuvOx Pharma[19] (USA) who are developing a therapeutic to treat diseases relating to hypoxia, and Membio[20] (Canada) who are working on biomanufacturing blood without a donor. Most clinical trials identified had no phase listed (n=6), three were in phase 1, and one each in phase 1/2 and phase 2. No study results were published on the clinical trial sources. Study inclusion conditions (Figure 1) focused on transplant (n=3), acute ischaemic stroke (n=2), followed by advanced solid tumour, anaemia, critical limb ischaemia, haemorrhage, healthy individuals and renal disease (n=1).

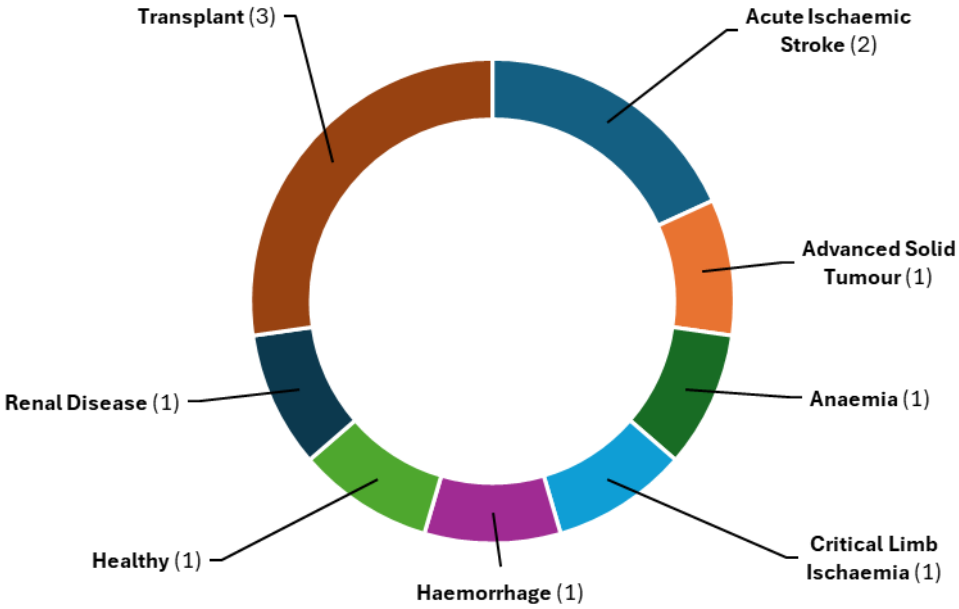

Figure 1. Conditions across the included clinical trials

Product	Condition(s)	Clinical trial ID(s)	Clinical trial status
ABL-101	Acute ischaemic stroke	NCT03463551	Unknown
HBOC-201	Anaemia	NCT01881503	Unknown
HEMO2life	Renal disease; transplant	NCT04181710; NCT05050513; NCT05469906; ACTRN12623000301662p	Completed; unknown; not yet recruiting; not yet recruiting
Whole blood analogue	Haemorrhage	NCT05756426	Recruiting
PP-007	Acute ischaemic stroke	NCT04677777	Completed
YQ23	Advanced solid tumour; critical limb ischaemia; Healthy	NCT04513067; NCT04792008; NCT03802292	Terminated; terminated; completed

Table 1: Artificial blood products by indication and stage

There were two UK-based clinical studies: one on YQ23 in healthy participants (phase 1, completed),[11] and another on ABL-101 for acute ischaemic stroke (phase 2, unknown).[12] The phase 2 clinical trial (POST-IT, NCT03463551) is sponsored by NHS Greater Glasgow and Clyde trust, collaborating with Aurum Biosciences. Its aim is to evaluate the safety and tolerability of three dose levels of ABL-101 and supplemental oxygen in acute stroke patients. By carrying substantial extra oxygen to the brain, the ABL-101 molecule may allow the visualisation of salvageable tissue and also prevent progression of stroke damage: this may have an additional direct benefit on tissue survival.[12]

A third randomised, controlled, phase 1 cross-over trial was identified, through contact with a clinical expert (in addition to those found via registry searches), called RESTORE (REcovery and survival of STem cell Originated REd cells).[21,22] Its aim is to assess the recovery and survival of a mini-dose of RBCs, derived from CD34+ cells isolated from adult blood, against standard

donated RBCs. It is hypothesised that manufactured RBCs will have a longer survival in circulation.

Funding landscape

We identified nine non-NIHR funding records for artificial blood projects, with five of these still ongoing. Whilst the highest number of funding grants was allocated by the NIH in the USA (five projects), the largest allocator of funds was the Wellcome Trust in the UK, who allocated £2,130,351 between two projects (Figure 2).[23-28] Of the nine funded projects, five were based in the USA,[25-28] three in the UK,[23,24,29] and one in Switzerland[30]. Four of the projects were led by industry sponsors with the rest being conducted by universities. All grants have been converted into GBP to allow comparisons, using May 2024 conversion rates.

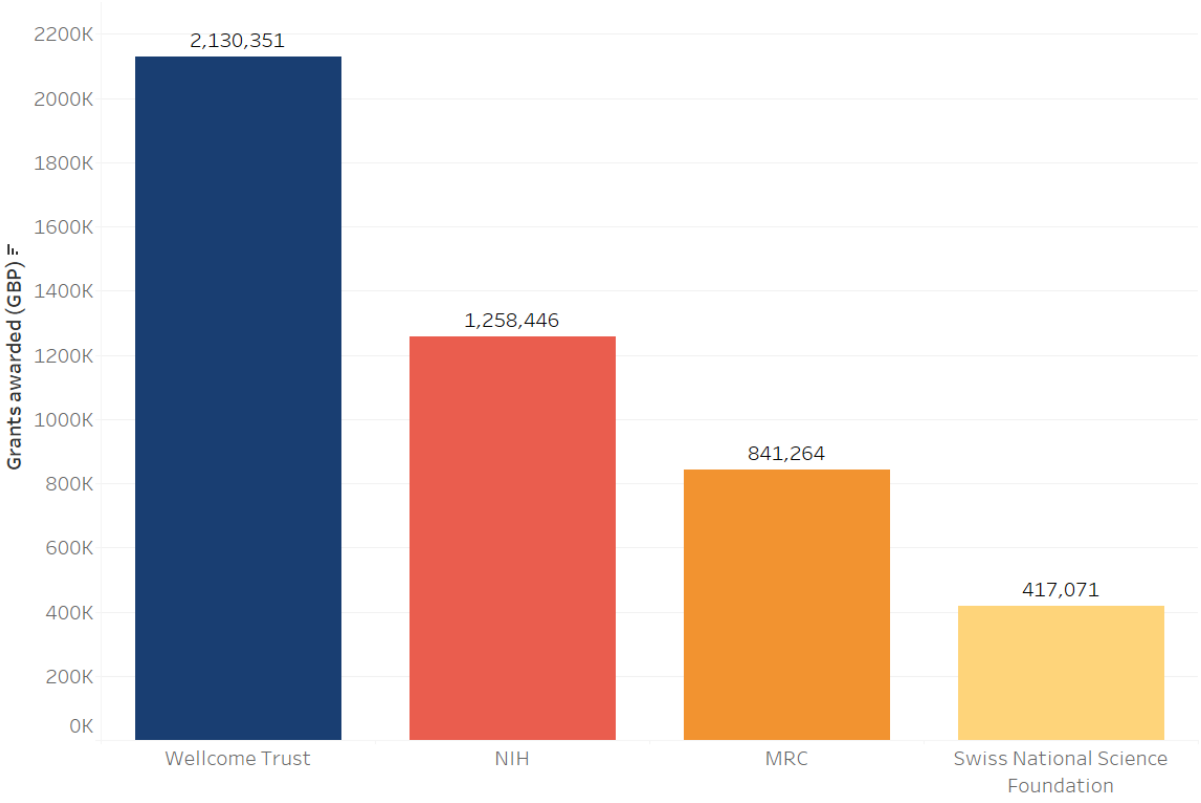

Figure 2. Graph showing the total amount of grants awarded by each funding body in GBP

The types of interventions studied included four on perfluorocarbon-based oxygen carriers, two on ErythroMer (Kalocyte, USA) or its precursor KC1003, two on GPI-ADAMTS13-Cultured Red Blood Cells and one project researching homogenous synthetic haemoglobin. Perfluorocarbon-based oxygen carriers received the highest combined level of funding, followed by Erythomer, homogenous synthetic haemoglobin and GPI-ADAMTS13-Cultured Red Blood Cells (Figure 3). The two projects for this latter technology started the earliest (2015) but no overall trend was seen in terms of type of intervention through time. There was also no

trend in funding amount with time, although most funding was awarded 2021-23 with one grant given in 2013, and two not reported.

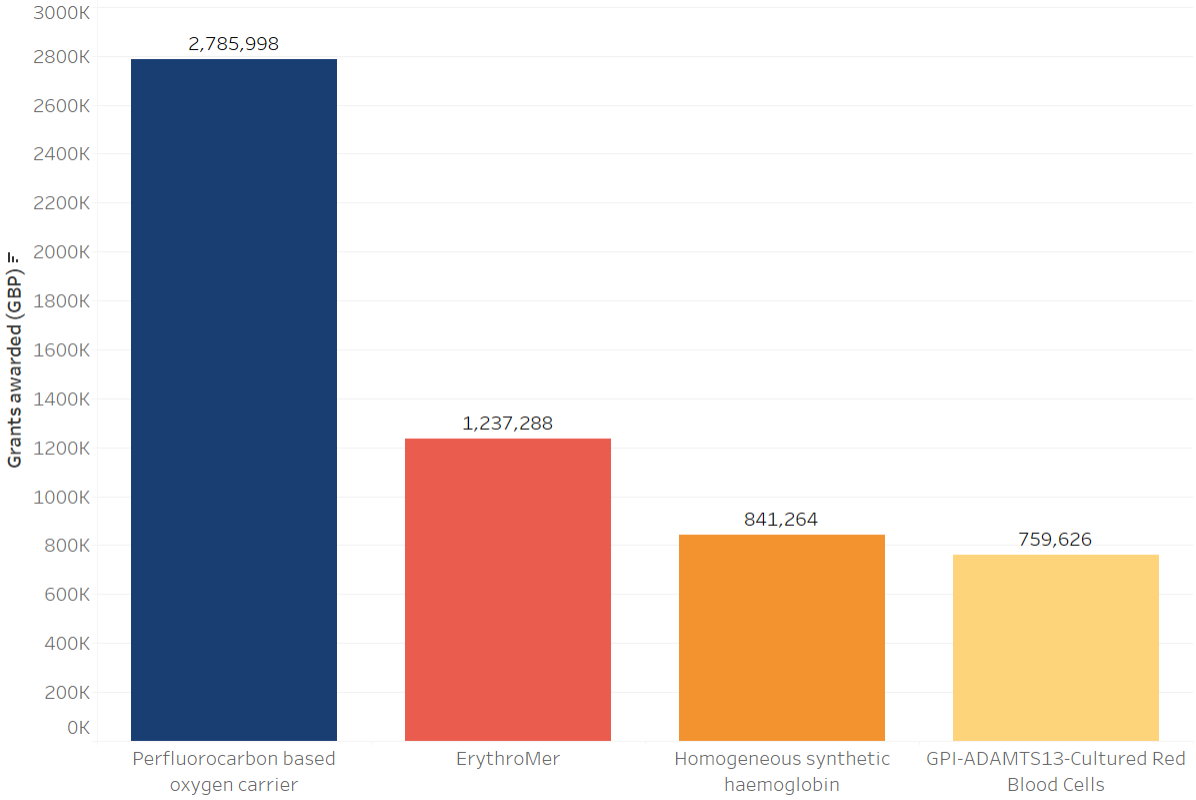

Figure 3. Level of funding awarded by technology type, shown as GBP

Published evidence

The following section identifies artificial blood products and their uses as reported in either clinical studies (in humans), *in vivo* preclinical studies or *ex-vivo* studies (involving animals or human/animal tissues). It also considers evidence from recent (published in 2023) literature reviews that implemented searches of bibliographic databases to identify studies on artificial blood products. The searches and screening were highly targeted to capture recent relevant evidence and are not comprehensive.

Literature reviews

Most research on HBOCs between 1991 and 2022 was undertaken in the USA, China, Europe, Canada and Japan.[2]

Hemopure (HBOC-201, HbO2 Therapeutics Corporation, USA) is the only commercially available HBOC that is used in human patients on a global scale;[2] Oxyglobin is approved for veterinary use in the European Union (EU) and the USA; HemO2life has recently been

approved for organ preservation in the context of transplantation in the EU; and OxyVita and Sanguinate are in clinical development. The following artificial blood products have been discontinued: HemAssist, PolyHeme, Hemolink, Hemospan, and Hemoximer.[1]

Clinical research

Clinical trials

Hemopure is an HBOC produced by polymerization of bovine Hb molecules. A retrospective analysis of clinical trial data compared mortality related to Hb deficit in patients who received Hemopure versus blood cells from human donors following orthopaedic surgery. No differences in mortality were found between groups. [31] In a separate analysis, the effectiveness of Hemopure for oxygen transportation was compared to packed red blood cells (red blood cells that have been removed from donor blood, to separate then from platelets and plasma) in human patients. The use of Hemopure was associated with a greater Hb deficit and with an increase in the number of severe adverse events compared to packed red blood cells.[32]

Hb vesicles (HbVs) are HBOCs incorporating purified and concentrated Hb solution in vesicles (fluid-filled sacs that are surrounded by a membrane). In a clinical trial, healthy male adults were injected with HbVs to assess the safety of this product and its effects on blood parameters. Adverse events observed were tolerable and spontaneously resolved and no clinically significant change was observed in any vital sign, including blood pressure.[33]

Case reports and case series

Hemopure and Sanguinate (another bovine-derived artificial oxygen carrier) have been used to treat bleeding and severe anaemia in cases where transfusion was indicated but not possible (e.g., due to religious beliefs).[34-40]

Hemopure has also been used to treat unconsciousness caused by acute severe anaemia in dying patients.[41]

A case report showed that inhaled nitric oxide allowed for the safe use of Hemopure infusion by preventing HBOC-induced pulmonary and systemic vasoconstriction. [42]

Preclinical research

In-vivo/ex-vivo studies

The viability and patient outcomes following transplantation of human livers perfused with oxygen transported by two different oxygen carriers was assessed: an artificial HBOC or RBCs (the specific HBOC used was not reported).[43]

The cardioprotective effects of perfusing hearts isolated from rats with St Thomas Solution versus polymerized Hb derived from human placental cells (PolyPHb) was compared.[44]

VS-101 is a HBOC derived from unused donated human red blood cells. The safety and ability of VS-101 to maintain circulatory function and capillary oxygen delivery in anesthetised, male Sprague Dawley rats was assessed.[45]

YQ23 is a bovine-derived HBOC formed by cross-linking tetrameric Hb. It was used to treat haemorrhagic shock in rats and pigs to assess its effects on survival, tissue and blood parameters and organ function.[46]

Discussion

A variety of artificial blood products, predominantly HBOCs, were identified that are at different stages of development. One of these (Hemopure, HBOC-201) is being used on a global scale, another (HemO2life, M101) has been approved in the EU to preserve organs for transplantation, and other products are being tested in clinical trials for the treatment of a range of conditions including cancer (YQ23) and acute ischemic stroke (Sanguinate, PP-007). Other products are being tested at the pre-clinical (animals and extracted tissues) stage. This illuminates the pipeline in artificial blood product development.

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This work was undertaken using a rapid approach. Although undertaken using a systematic approach, processes within the cycle of conducting a horizon scan have all been abbreviated, limiting our certainty about the evidence presented; ultra rapid evidence synthesis approaches have been used to consider the published literature. There has been no formal quality assessment of the information included within this innovation briefing and no quality assurance processes have been undertaken as part of the methodological approach.

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