World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 6.129

THE DEVELOPMENT OF ARTIFICIAL BLOOD. A REVOLUTIONARY BREAKTHROUGH IN MEDICINE

Maria San Miguel[1], Daniel Garcia Moreno[2], Angel San Miguel[3*] and Julia San Miguel[1]

[1]Research Unit. Rio Hortega Valladolid. University Hospital. Spain.
[3]Health Center, Ribera Del Orbigo. León. Spain.
[2]Clinical Analysis Service. Rio Hortega Valladolid. University Hospital. International University of La Rioja (UNIR). Spain.

***Corresponding Author: Dr. Angel San Miguel**
Universidad Internacional de la Rioja (UNIR).

Article Received on 20/06/2023 **Article Revised on 10/07/2023** **Article Accepted on 31/07/2023**

SUMMARY

Artificial blood is a field of research that seeks to develop synthetic substitutes for human blood. These substitutes are intended to provide an alternative to real blood in emergency situations, supply shortages, or when real blood is not compatible with the recipient. Advances in bioengineering, biotechnology and nanotechnology have led to significant progress in the development of artificial blood. Research has been conducted to improve the functionality and safety of blood substitutes, such as modifications to hemoglobin to improve its oxygen-carrying capacity, the use of nanomaterials to encapsulate hemoglobin substances and improve their stability, and cell production. synthetic blood in the laboratory. However, the development of artificial blood also raises challenges and ethical considerations. Extensive testing is needed to assess the safety and efficacy of blood substitutes, address concerns related to immunological compatibility and adverse reactions, establish scalable and affordable manufacturing processes, and ensure equitable and ethical access to artificial blood. Despite these challenges, artificial blood is expected to become a clinical reality in the future, providing a valuable and reliable option in the medical field and improving medical care in critical situations.

KEYWORDS: artificial blood, challenges, development.

INTRODUCTION

Blood is a vital component for the proper functioning of the human body, carrying oxygen and nutrients to tissues, removing waste, and playing a crucial role in the immune response. However, there is a constant need for blood in hospitals and medical centers around the world, which has led to a chronic shortage of donors and the need to search for alternatives. In this context, the development of artificial blood has emerged as a promising solution that could revolutionize the field of medicine.

Chronic blood shortages have been a persistent problem around the world. Blood banks and hospitals often face shortages of blood supplies, especially during emergencies or natural disasters. In addition, the different blood groups and possible immunological incompatibilities make it difficult to have compatible blood available for all patients.[1-3]

Artificial blood is a fascinating field of research that seeks to create a synthetic substitute for human blood. Although royal blood is a valuable and vital resource, donor shortages and storage and transportation limitations have led to the need to seek innovative alternatives. Artificial blood has the potential to overcome these challenges and revolutionize the field of medicine by providing a reliable and safe source of blood.

In addition to addressing the donor shortage, artificial blood could also offer significant benefits in terms of storage and transportation. Real blood requires specific storage and transportation conditions, such as low temperatures and limited shelf life. These limitations can be especially challenging in remote areas or in emergency situations where it is not possible to access a source of fresh blood quickly. Artificial blood, being a synthetic product, could have a longer shelf life and be easier to store and transport, which would facilitate its distribution and availability in critical places and at crucial times.[4-6]

The development of artificial blood also has the potential to reduce the risks associated with blood transfusions, such as blood-borne infections or adverse immunological reactions. Being a product created in the laboratory, its quality and safety can be guaranteed, which can reduce the risks inherent in conventional transfusions.

However, despite all the advances and potential benefits, it is important to recognize that the development of artificial blood is still at an early stage and faces several technical and ethical challenges. Precise replication of the complex functions of human blood, such as oxygen and nutrient transport, coagulation, and immune responses, remains a significant challenge.

Over the years, scientists and researchers have been hard at work developing methods and technologies that allow for the creation of functional artificial blood. The main purpose of artificial blood is to provide a safe and effective alternative to real blood in critical situations where the blood supply is insufficient or unavailable, such as in natural disasters, armed conflict, or in remote areas with limited access to medical facilities.[7-10]

The development of artificial blood has become a multidisciplinary field that combines bioengineering, biotechnology, nanotechnology and regenerative medicine. Advances in these areas have paved the way for the creation of artificial blood components, such as modified hemoglobin substances and synthetic blood cells, which have the ability to perform crucial functions of human blood.

As technological advances continue to accelerate, it is necessary to take a closer look at recent progress in the development of artificial blood, as well as the challenges and ethical considerations associated with this innovative technology. By doing so, we can better understand the potential and limitations of artificial blood and its impact on modern medicine (Figure 1).

Figure 1: Artificial blood.

The continuous need for blood and the difficulty to fully satisfy it have led to the search for innovative alternatives. In this context, the development of artificial blood has emerged as a promising solution that could revolutionize the field of medicine.[11-15]

The development of artificial blood is an exciting and promising field of research that seeks to provide a solution to blood shortages and improve healthcare. As scientists continue to explore and refine techniques, we may see significant advances in the production and application of artificial blood in the near future, which could have a lasting, positive impact on modern medicine.

ARTIFICIAL BLOOD

Artificial blood is a synthetic substitute for human blood that is created in the laboratory for the purpose of replicating the essential functions of real blood. Unlike real blood, which comes from human donors and is subject to availability and compatibility limitations, artificial blood is produced through controlled engineering and manufacturing processes.

Artificial blood is made up of various components designed to mimic the fundamental functions of human blood. These components may include modified hemoglobin substances, synthetic blood cells, artificial plasma, and coagulation factors.[16-20]

One of the key aspects in the development of artificial blood is the ability to carry oxygen. Hemoglobin, a protein found in red blood cells, is responsible for carrying oxygen from the lungs to the tissues of the body. In artificial blood, modified hemoglobin substances are used that can bind and release oxygen efficiently.[20-23]

In addition, it also seeks to replicate other functions of real blood, such as the supply of nutrients to tissues, the removal of metabolic waste, and the immune response. To accomplish this, researchers are exploring the development of synthetic blood cells, such as red blood cells and white blood cells, that can perform these essential functions.

Artificial blood also addresses the concern of blood compatibility, as it can be manufactured with universal characteristics, thus avoiding the need for cross-compatibility testing prior to use in transfusions. This could be especially beneficial in emergency situations, where time is of the essence and compatibility testing can delay the medical care process.[24-28]

Thus, artificial blood is a laboratory-created substitute that seeks to mimic the essential functions of human blood. Through the use of modified hemoglobin substances, synthetic blood cells, and other components, artificial blood is expected to offer a safe and effective alternative to real blood, thus addressing the challenges of availability, compatibility, and risks associated with conventional blood transfusions.

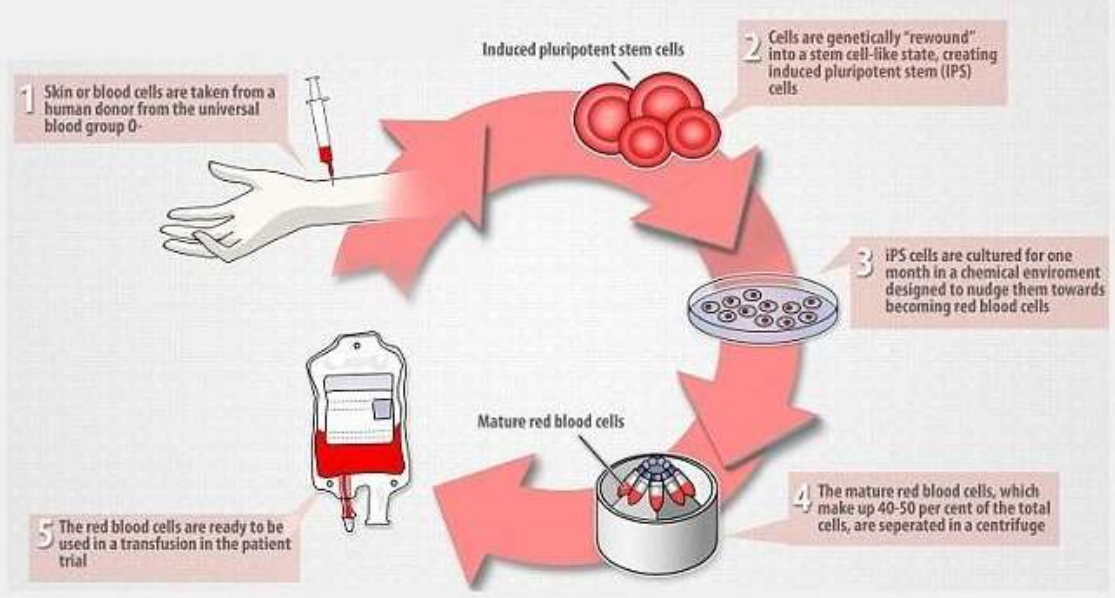

Figure 2: Artificial blood substitutes.

TYPES OF BLOOD SUBSTITUTES

Different blood substitutes have been developed and are classified by differentiating them. according to the nature of the molecule that transports oxygen.

-Oxygen carriers based on perfluorocarbonates (PFC), which, in turn, we classify as first, second and third generation perfluorocarbonates,

-Oxygen carriers based on hemoglobin and are classified into first, second, and third generation, PEGylated hemoglobin and encapsulated hemoglobin.

-And the Plasmatic Superexpanders that are useful to delay a blood transfusion.

1. OXYGEN CARRIERS BASED ON PERFLUOROCARBONATES

Perfluorocarbonates are molecules synthetics composed only of carbon and fluorine. The interaction between these atoms forms a strong and long bond, which protects the molecule from degradation. Because of their hydrophobicity, a complicated procedure was devised to stabilize them in an emulsion for intravenous use, which can dissolve gas better than most liquids.

PFCs have strong intramolecular bonds that make them stable, but their intermolecular bonds are very weak, which is why they behave like gaseous fluids that dissolve other less cohesive substances, such as oxygen or carbon dioxide, which is why they are capable of transporting these gases without joining them.[13,23]

- 1st generation PFC. Fluosol-DA; It is available in a 20% solution, with the ability to carry 7.2% O2 at 37C, or 34% at a hemoglobin level of 14 g/ dL. Its use was in patients with gastrointestinal bleeding and blood loss related to surgery for esophageal cancer. Subsequent *in vivo* and *in vitro* clinical trials studied its use in patients with different problems, such as severe anemia, peripheral vascular disease, and massive blood loss from surgical wounds.[23]

- 2nd generation PFC. OxygentTM, consisting of two active ingredients, perfluorooctyl bromide and perflubrodec. It is stable at room temperature for a few weeks, and has a shelf life of 24 months when stored at 2-8 C. Numerous preclinical studies were conducted to understand its safety in different animal species before moving to human studies. In Europe, a Phase II multicenter study showed that combined with anticoagulants may reduce the need for red blood cell transfusion.

- 3rd generation of PFC. OxycyteTM, which is emulsified with purified egg yolk phospholipids. It was tested in phase II trials with patients suffering from traumatic brain injury, unfortunately there are currently no publicly available data for this trial, but the company stated that it achieved its original goal of increasing the arterial blood oxygen partial pressure level su use was suspended.[8,9]

2. HEMOGLOBIN-BASED OXYGEN CARRIERS[29-31]

Natural hemoglobin is a globular protein with a quaternary structure, formed by two alpha subunits and two beta subunits, linked to a heme group with a central iron atom to which an oxygen molecule is linked. The binding of oxygen to the heme group results in a conformational change in the hemoglobin molecule, which causes the affinity of the other subunits for oxygen to increase, and vice versa. Therefore, free hemoglobin can be used as a blood substitute, since it maintains its oxygen-carrying capacity outside of red blood cells, however, it is quite toxic to surrounding tissues, since hemoglobin captures nitric oxide endothelial and leads to vasoconstriction and development of oxygen free radicals.

In addition, the hemoglobin molecule requires the presence of 2,3-bisphosphoglycerate to deliver oxygen to the tissues, therefore, free hemoglobin in the absence of this compound is ineffective.[23]

When the hemoglobin molecule becomes dysfunctional, its affinity for oxygen increases and it loses the ability to release it to the tissues, producing oxidation that transforms it into methemoglobin. The hemoglobin derivatives developed have to undergo stability improvement techniques, to prevent their passage to methemoglobin. According to the applied techniques we can find different groups.

- 1st generation of HBOC. Stromal-free hemoglobin (SFH) products, these were prepared from lysis of packed erythrocytes by ultrafiltration or crystallization. The erythrocyte stroma acts as an antigen, which when combined with the corresponding receptor antibodies can cause disseminated intravenous coagulation and renal failure, whereby, when the stroma is removed, the hemoglobin solution becomes a relatively nontoxic product. Ultrafiltration preparations are characterized by a lower content of protein components and residual membrane phospholipids. On the contrary, those produced by crystallization presented a less favorable result, giving a less purified product with a higher content of phospholipids and proteins , which can cause protein aggregates during storage, or vasoconstrictive and depressant actions on contractility.[23]

- 2nd generation HBOC. They are pyridoxylated conjugates of hemoglobin polyoxyethylene (PHPC), prepared from the SFH. These were designed to prevent major disadvantages, such as increased oxygen affinity, short circulatory half-life, and nephrotoxicity. What is done is that the free hemoglobin of the HPS is pyridoxylated adding vitamin B6 to adjust the oxygen affinity of hemoglobin and is conjugated with α-carboxymethyl-ω-carboxymethoxypolyethylene, in order to increase the molecular weight and ensure a longer circulatory half-life go away.

PolyHemeR and HemopureR (HBOC-201) were developed, but only HemopureR has been approved by the FDA for compassionate use as many of these products have shown adverse effects in clinical trials multicenter trial investigating safety and efficacy in patients undergoing non-cardiac surgery found that the use of HBOC products can reduce red blood cell transfusion in 43% of patients with no difference in mortality and serious adverse effects. Instead. showed an excess of mild adverse effects, such as hypertension and fever, for this reason , it can only be used in case of need to treat severe anemia that threatens the patient 's life.[31]

- 3rd generation HBOC. They are hemoglobin polymerized with dibromosalicyl fumarate or aa-hemoglobin. HemAssistR was one of those developed with a diaspirin cross-linked hemoglobin (DCLHb), which was more homogeneous to withstand toxicological and physiological experiments and presented oxygen affinity similar to that of blood. They were prepared using human or bovine blood, washing the erythrocytes with sterile saline solution to remove traces of plasma and subsequently subjecting them to hypertonic lysis. They were then filtered and purified hemoglobin was obtained with an overall yield of 58%. This product can be stored at -20 C for one year.[28] In contrast, these products lack the ability to regulate the oxidative state caused by heme iron, and phase III trials have shown higher mortality. More recently it developed HemoLinkTM, which has been successfully tested in Phase I and Phase II trials in patients undergoing coronary artery bypass graft surgery.

PEGylated hemoglobin

Pegylation consists of the union of a polyethylene glycol (PEG) to hemoglobin, generating a very stable derivative that receives the generic name of pegylate (Figure 3). After several failed clinical trials of HBOC, the evidence was clear that these products are not clinically and biochemically identical to human hemoglobin. So it was difficult to get approval for subsequent clinical trials in humans.

Scientists have shifted focus towards developing oxygen bridging agents that can be used in situations where blood is not available for red blood cell transfusion and have since changed their name to Oxygen Therapeutic Agent (OTA), whose essential characteristics are greater affinity for oxygen, minimum uptake of nitric oxide, and present a greater molecular size and chemical homogeneity.

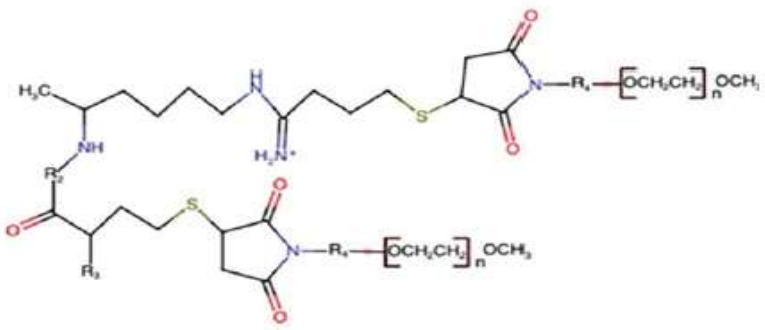

Figure 3: Oxygen therapeutic agent based on pegylated hemoglobin.[23]

There are two pegylated hemoglobin oxygen carriers developed, HemospanR and Sanguinate R.

- Hemospan (MP4), is a human hemoglobin-based agent that was developed to mediate the vasoactive and hypertensive effects of previously developed PEGylated hemoglobin molecules. The clinical efficacy and safety of Hemospan were evaluated in a multicenter study and did not report any clinically significant adverse events, and the frequency of antihypertensive episodes was low, although transient increases in liver enzymes were observed in patients undergoing major orthopedic surgery. This study speculates that it may be more useful in clinical settings that require rapid oxygen delivery to ischemic tissues. Some phase II studies were conducted in the US and phase III studies in Europe, on the contrary, no official data has been reported by the research manufacturer on the clinical efficacy and safety of the product so far.[15]

- Sanguinate, is an oxygen therapeutic agent PEGylated and hybridized with carbon monoxide (PEG- COHb), with modes of action useful for mitigating the limitations of previous generations of HBOC. It is being studied for its characteristics, vasodilator and non-inflammatory properties.[27] PEG- COHb is a modified bovine hemoglobin. In an "in vitro" model, it has shown that its polymerization and carboxylation have the potential to rapidly release carbon monoxide and increase the storage of carboxylated hemoglobin in whole blood. This allows oxygen to bind to the carbon monoxide site under hypoxic conditions and ultimately oxygenates the end organs.[13] The FDA has granted orphan drug status for the treatment of sickle cell anemia.

- Encapsulated hemoglobin

They are encapsulated hemoglobin liposomes, where the purified hemoglobin is re-encapsulated in a stable lipid membrane and this allows manipulation of its physicochemical properties and circulation lifetime. In addition, it prevents the denaturation of hemoglobin and improves biodistribution.

3. PLASMA SUPER EXPANDERS

They are not in themselves blood substitutes, since they do not act as oxygen carriers. They are used to delay red blood cell transfusion and restore microvascular function. These super expanders They act as the initial replacement of the blood volume deficit after its loss, but they will only be used when the availability of oxygen carriers does not decrease, with the aim of maintaining blood pressure.

The composition consists of the conjugation of albumin with polyethylene glycol and alginates. Polyethylene glycol-conjugated albumin and high molecular weight alginates are effective in maintaining capillaries functioning under conditions of extreme hemodilution. This is because they increase the viscosity of the plasma, compensating for the loss of blood viscosity. The elevation of plasma viscosity in the presence of a decrease in blood viscosity maintains the pressure in the circulation, because the loss of pressure in the great vessels decreases and the pressure is transmitted to the peripheral and capillary vessels, thus avoiding their collapse due to hypotension.

In the physiological process of hemorrhage and erythrocyte loss, the intrinsic oxygen transport capacity decreases and there is a drop in blood pressure with an increase in vascular tone, so these super-expanders are beneficial at the beginning of the loss because they reduce the viscosity, causing a very important change in the mechanical conditions of circulation.

These blood substitutes have a series of limitations, which restrict their use.

PFCs are responsible for the activation of the complement system, showing cytotoxicity in cells . Phagocytic, such as monocytes and granulocytes. With flu-like symptoms, due to opsonization (the process by which antibodies mark a pathogen for ingestion and destruction by a phagocyte) and phagocytosis of the PFC emulsion by the immune system of the recipient organism. Another adverse effect that they present is the transient reduction of the platelet count.

Not being able to be used by the organism, they are slowly excreted, causing an overload in the reticuloendothelial system and a suppression of its function, in the same way that they can be accumulated in the organs. So Fluosol was removed from the market. The second generation also presented problems with oxygen delivery, this being insufficient, even requiring supplemental oxygen inhalation. Because of failures in initial trials, but some products such as PERftoranR and VidophorTM They are being used in some countries.

As for HBOCs, they also have drawbacks, since free hemoglobin has drawbacks, it is toxic to the surrounding tissues, since it includes endothelial uptake of nitric oxide, producing vasoconstriction and development of free radicals, leading to tissue hypooxygenation and the consequent systemic and pulmonary hypertension. This is due to the fact that free hemoglobin diffuses through the arteriolar wall, increasing local oxygenation, and although red blood cells do not reach that localized area, this increase in partial pressure of oxygen is interpreted by the arteriolar wall receptors as a result of excessive flow. of blood, to which they respond by triggering a vasoconstriction. Therefore, hemoglobin has to undergo bioengineering processes to overcome these drawbacks and obtain useful modified hemoglobin solutions. These processes lead to an increase in the half-life of the modified hemoglobin in the plasma thanks to the conjugation of the dimers, polymerization of the molecules among themselves and modification of the surface with dextran. With this, it is possible to hide the molecule from the reticuloendothelial system and

provide an affinity curve for oxygen similar to that of intraerythrocytic hemoglobin. An advantage of modified hemoglobin is that it can be obtained from expired human blood, bovine blood, or through genetic recombination, as it does not require compatibility testing before infusion, can be sterilized at low temperature, and may have a long shelf life. Despite everything, some of the derivatives have had to be abandoned after phase III trials, due to the presence of serious and unexpected toxicity.

All blood substitutes have benefits and drawbacks, but thanks to them, the costs of analyzing and treating blood from donors are saved, but because they are still in development they involve research costs, which are higher . As long as blood donations continue to exist, it will be more efficient than using blood substitutes and due to the total absence of safety.

- OBTAINING RBCs FROM THE CULTURE OF EMBRYONIC STEM CELLS

It is a potential source of obtaining mature erythrocytes with the capacity to transport oxygen on a large scale, this is because these cells behave like mature red blood cells.

The method used consists of the generation and expansion of erythrocytes from a culture of human embryonic stem cells, for this, embryonic cell lines are used and the following steps are carried out. First, the formation and expansion of hemangioblasts (cells that give rise to cells) are induced. hematopoietic cells) and their differentiation into erythroid cells. Next, the identification of functional erythrocytes is performed, and finally, with the help of vitamin B12 and folic acid, mature red blood cells are obtained.

oxygen dissociation curves of the hemoglobins obtained show a very similar response to those of normal adult red blood cells, although the response to 2,3-bisphosphoglycerol is somewhat less. This allows us to verify that the red blood cells obtained by this method have oxygen -carrying properties.

Since the cells obtained have little hemoglobin formed by beta chains, which are the ones that release oxygen more easily. And also with this method, relatively few cells without antigenic determinants are obtained , from group 0 Rh negative (universal donors). In addition, its efficacy and safety "in vivo" are yet to be demonstrated, and the existing moral and ethical debate for the use of human embryonic cells, since each country has different legislation.

***-ErythroMer* Study**

ErythroMer belongs to the group of Oxygen Therapeutic Agent (OTAs). The term refers to a component that can replace blood, although it only has a 10% coincidence with red blood cells, researchers believe that it would serve to stabilize patients in Emergency Services.

This product presents a promising approach, since it can simulate the interaction normal physiology of red blood cells with oxygen and nitric oxide. In addition, it is designed in powder form and made up of artificial cells that fulfill the same functions as red blood cells, it only needs to be mixed with sterile water to be injected and it can be stored at room temperature.

There are other products, such as OxyVitaR, which is a stroma-free cross-linked bovine hemoglobin, HbVesicles, liposome-encapsulated hemoglobin and HemoAct, human hemoglobin that is related to albumin molecules.[20]

ADVANCES IN THE DEVELOPMENT OF ARTIFICIAL BLOOD

In recent years, there have been significant advances in the development of artificial blood, thanks to the combination of bioengineering, biotechnology and other scientific disciplines. These advances are focused on improving the functionality, safety, and availability of artificial blood. Some of the most notable advances include.

- Modified hemoglobin substances. Scientists have succeeded in modifying the structure of hemoglobin, the protein responsible for transporting oxygen in the blood, to improve its stability and ability to bind and release oxygen. These modified hemoglobin substances can be encapsulated in microcapsules or nanoparticles to prolong their useful life and prevent their rapid degradation in the bloodstream.

- Nanotechnology. Nanotechnology has played an important role in the development of artificial blood. Nanomaterials, such as carbon nanotubes and nanospheres, are used to encapsulate hemoglobin substances and improve their stability and efficiency in oxygen transport. In addition, nanosensors are being investigated to monitor and regulate the release of oxygen in the body, ensuring adequate delivery according to metabolic needs.

- Synthetic blood cells. Efforts are underway to develop synthetic blood cells in the laboratory. These cells could be designed to fulfill specific functions, such as oxygen transport or immune response. Researchers are exploring various strategies to produce synthetic red blood cells that can perform a function similar to that of natural red blood cells.

- Artificial plasma. In addition to red blood cells, plasma is an essential component of blood. Artificial plasma, made up of a solution of proteins, salts, and other compounds, is being investigated to replace or supplement real plasma in emergency situations. Artificial plasma can help maintain blood volume and provide the necessary nutrients for proper tissue function.

- 3D printing of blood tissues. 3D printing technology is being explored to create blood tissues in the laboratory. Methods are being investigated to print functional capillaries and blood vessels, which would allow the creation of more complex structures and the manufacturing of blood tissue on a large scale.

Figure 4 shows artificial blood vessels created with 3D bioprinting technology.

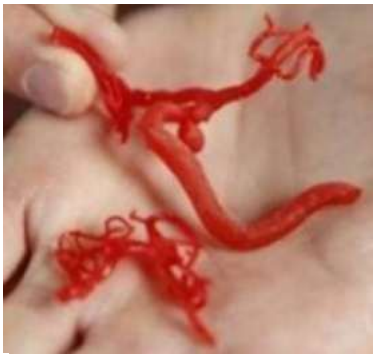

Figure 4: Artificial blood vessels created with 3D bioprinter technology.

Although these advances are promising, there are still significant challenges in the development of artificial blood. These include the need for extensive safety and efficacy testing, ensuring immunological compatibility, addressing durability issues, and establishing efficient and scalable manufacturing processes. As researchers continue to work in these areas, it is hoped that artificial blood will become a clinical reality and provide a valuable and reliable alternative to real blood in the future.

Artificial blood stored in powdered form could one day revolutionize emergency medicine and give trauma victims a better chance of survival. The synthetic product could save lives on the battlefield, remote areas.

Researchers have created an artificial red blood cell that effectively picks up oxygen in the lungs and delivers it to tissues throughout the body. This artificial blood can be freeze-dried, making it easy to have in an emergency.

Figure 5 shows schematically and graphically the method for obtaining mature red blood cells from a universal donor (O-).

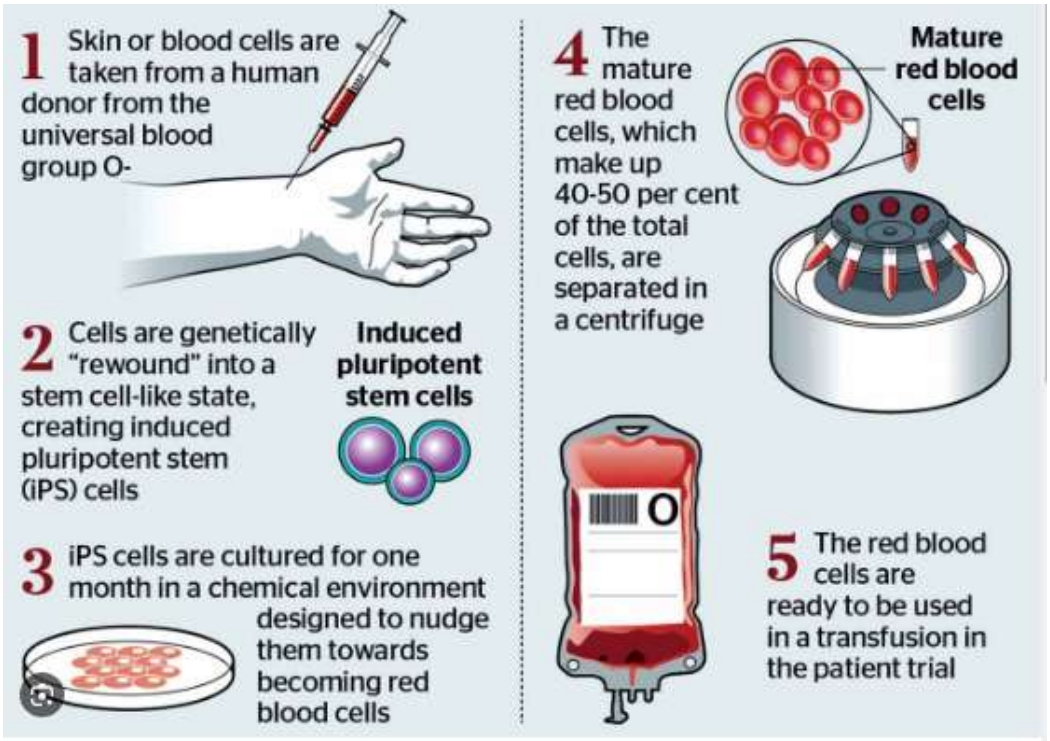

Figure 5: Schematic of the method for obtaining mature red blood cells, from a universal donor (O-).

Figure 6 summarizes the benefits of using artificial blood.

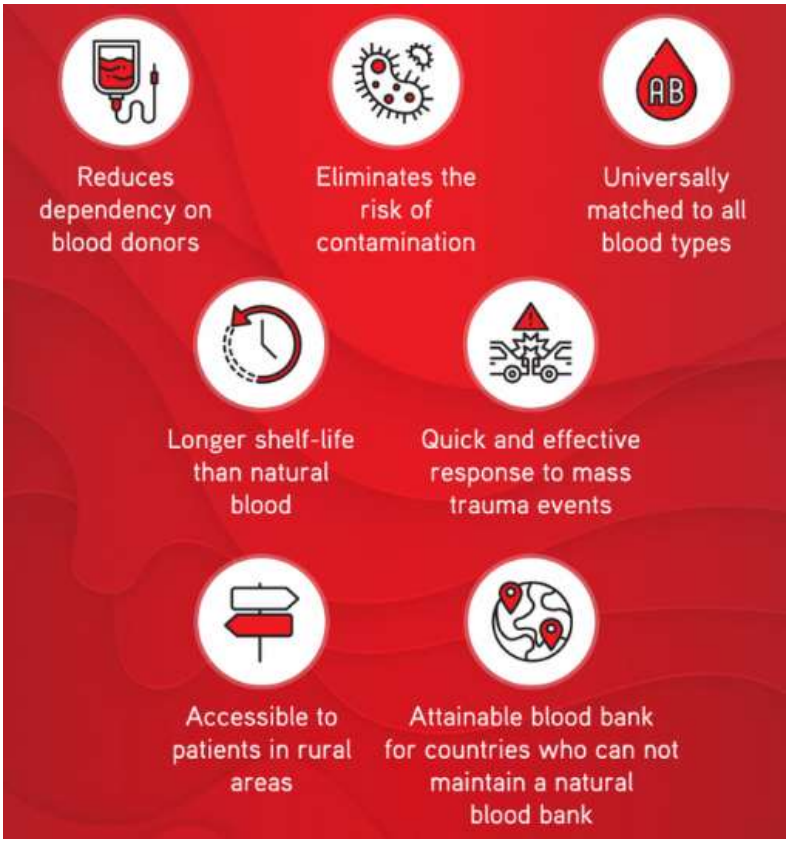

Figure 6: Benefits of using artificial blood.

CHALLENGES AND ETHICAL CONSIDERATIONS

While the development of artificial blood offers great potential, it also raises challenges and ethical considerations that need to be properly addressed. Below are some of the most prominent challenges.[15,19,20,23]

- **Safety and efficacy.** Before artificial blood can be widely used in clinical settings, rigorous testing is necessary to assess its safety and efficacy. It is critical to ensure that artificial blood does not cause adverse reactions, such as excessive clotting or undesirable immune responses. Furthermore, the artificial blood must have efficacy comparable to real blood in terms of oxygen transport, nutrient delivery and immune response.

- **Compatibility and immunological reactions.** Blood compatibility is a critical challenge in the development of artificial blood. Unlike real blood, which is tested for compatibility before a transfusion, artificial blood must be matched to any given patient, which poses significant immunological challenges. Special attention is required to ensure that artificial blood does not trigger adverse immune responses, such as rejection or systemic inflammation.

- **Scale of production and costs**: The large-scale production of artificial blood is a significant technical and logistical challenge. To meet global demand, it would be necessary to establish efficient and scalable manufacturing processes. Additionally, the costs associated with the production of artificial blood could be an obstacle, especially considering its accessibility and availability in resource-constrained healthcare settings.

- **Ethical and social considerations.** The development and implementation of artificial blood also raise ethical and social issues. Intellectual property and the commercialization of artificial blood can create barriers to its equitable access and can generate inequalities in the distribution of this vital resource. It is critical to address these ethical concerns and ensure that artificial blood is available and affordable to all who need it.

- **Impact on blood donation.** If artificial blood becomes a viable alternative, it could have a significant impact on the blood supply of human donors. While this could alleviate blood shortages and reduce reliance on donations, it could also negatively affect blood banks and voluntary donor communities, requiring a reassessment of current systems and practices.

The development of artificial blood represents a promising scientific and medical advance, but also poses ethical challenges and dilemmas that must be addressed responsibly. It is crucial that researchers, scientists,

clinicians, and policymakers work together to overcome these challenges and ensure that artificial blood is developed and deployed in a safe, equitable, and ethical manner to improve healthcare and save lives.

CONCLUSIONS

The development of artificial blood is an exciting field of research that has the potential to revolutionize medicine and address the challenges associated with the supply of real blood. As advances in bioengineering, biotechnology, and nanotechnology continue, significant progress has been made in creating synthetic substitutes for human blood.

Artificial blood offers potential benefits, such as immediate availability, universal compatibility, and elimination of the risk of infectious disease transmission. Furthermore, it can be a valuable solution in emergency situations, armed conflicts or in remote areas with limited access to medical facilities.

However, there are still technical and ethical challenges that need to be addressed before artificial blood can be widely used. It is essential to ensure the safety and efficacy of artificial blood, as well as to address concerns related to immunological compatibility and adverse reactions. In addition, scalable manufacturing processes and affordable costs must be established to ensure the availability and accessibility of artificial blood.

Likewise, it is essential to consider the ethical and social implications associated with artificial blood. Equity in access, responsible marketing, and the impact on blood donation all need to be carefully addressed to ensure that artificial blood benefits all of humanity fairly.

Despite the challenges, the progress in the development of artificial blood is encouraging and shows the potential of this innovation to save lives and improve healthcare around the world. With continued collaboration between scientists, clinicians, ethicists, and policy makers, it is possible to overcome obstacles and move toward a reality where artificial blood is a viable and safe option in emergency and blood transfusion situations. Artificial blood has the potential to be a transformative tool in medicine, driving significant advances in healthcare and providing hope to those in need of a reliable blood supply.

REFERENCES

1. Natanson C, Kern SJ, Lurie P, Banks SM, Wolfe SM. Cell-free hemoglobin-based blood substitutes and risk of myocardial infarction and death: a meta-analysis. NEVER, 2008; 299(19): 2304-2312. doi:10.1001/jama.299. 19.jrv 80002.
2. Winslow RM. Blood Substitutes: Physiological Basis of Efficacy. Boca Raton, FL: CRC Press, 2017.
3. Intaglietta M, Winslow RM, Tompkins RG. Blood Substitutes: Principles, Methods, Products, and Clinical Trials. New York, NY: Springer Science & Business Media, 2012.
4. Ekdahl KN, Lambris JD, Elwing H, Ricklin D, Nilsson PH, Teramura Y. Innate immunity activation on biomaterial surfaces: a mechanistic model and coping strategies. Adv Drug Deliv Rev, 2011; 63(12): 1042-1050.
5. Buehler PW, Alayash AI. Blood Substitutes: New Challenges. San Diego, CA: Academic Press; 2013.
6. Roche CJ, Cantrill SV, Stansbury L, et al. Hemopure: a review of the clinical trials with a blood substitute. J Trauma, 2002; 52(2): 331-342.
7. Pietersz RN, Reesink HW, Panzer S, Wendel S, Eastlund T. Biochemical and functional characterization of hemoglobin-based oxygen carriers (HBOC) after radical and non-radical cross-linking. Vox Sang, 2009; 96(3): 206-218.
8. Simoni J, Simoni G, Moeller JF. Artificial blood. San Rafael, CA: Morgan & Claypool Life Sciences, 2012.
9. Chang TM. Artificial blood. Singapore: World Scientific Publishing, 2017.
10. Gómez- Lechón MJ, Tolosa L, Conde I, Donato MT. Competition of different cellular models to predict human hepatotoxic drugs. Expert Opin Drug Metab toxicol, 2014; 10(11): 1553-1568. doi:10.1517/17425255.2014.965247.
11. Rhee P, Brown C, Martin M, et al. QuikClot® Combat Gauze® use for hemorrhage control in military trauma: January 2009 Israel Defense Force experience in the Gaza Strip--a preliminary report of 14 cases, 2009; 24(5): 422-429. doi:10.1017/S1049023X00006968.
12. Guan J, Chan C, Zhang S, et al. Human embryonic stem cell-derived progenitors aid functional thymic regeneration in adult hosts. Blood, 2017; 130(Suppl 1): 1905.
13. Abuchowski A. SANGUINATE (PEGylated Carboxyhemoglobin Bovine): Mechanism of Action and Clinical Update. Artif Organs, 2017; 41(4): 346-350.
14. Benjamin RJ, McLaughlin LS. Plasma components: properties, differences, and uses. Transfusion, 2012; 52: 9-19.
15. US National Library of Medicine NCBI: National Center for Biotechnology Information . Available at: https://www.ncbi.nlm.nih.gov/books/NBK279392/
16. ROI flowers. Principles of Transfusion Practice. In: Carrillo ER, Perez C, AA. Transfusion Medicine in the Perioperative Clinics Mexicans of Anesthesiology. Editorial Alfil Mexico, 2016; 28: 1-12.
17. Mer M, Hodgson E, Wallis L, Jacobson B, Levien L, Snyman J et al. Hemoglobin glutamer-250 (bovine) in South Africa: consensus usage guidelines from clinician experts who have treated patients. Transfusion, 2016; 56(10): 2631-2636.

18. Gasparoni A, Ciardelli L, Avanzizni MA, Bonfichi M, Di Mario M, Piazzi G, Martinitti L, Vanelli L, Rondini G, Chirico G. Immunophenotypic changes of fetal cord blood hematopoietic progenitor cells during gestation. Pediatric research, 2020; 47: 825-829.
19. Haldar R, Gupta D, Chitranshi S, Singh MK, Sachan S. Artificial Blood: A Futuristic Dimension of Modern-Day Transfusion Sciences. Cardiovasc Hematol Agents Med Chem, 2019; 17(1): 11-16.
20. Gekka M, Abumiya T, Komatsu T, Funaki R, Kurisu K, Shimbo D et al. Novel Hemoglobin-Based Oxygen Carrier Bound With Albumin Shows Neuroprotection With Possible Antioxidant Effects. Stroke, 2018; 49(8): 1960-1968.
21. Hussen KA, Chabaane E, Canque B. Organization bipartite de la lymphopoiese humaine . Med Sci (Paris), 2018; 34: 665-670.
22. Kiu Y, Chan V. Artificial Blood: Current development and challenges. [online]. Imperial Bioscience Review, 2020. Available at: https://imperialbiosciencereview.com/2020/11/13/artificial-blood-currentdevelopment-and-challenges/
23. Khan F, Singh K, Firedman MT. Artificial Blood: the history and current perspectives of blood substitutes. Discoveries, 2020; 8(1): 1-15.
24. Shaffer L. Making and storing blood to save lives. News Features, 2020; 117(14): 7542-7545.
25. Mackenzie CF, Dube GP, Ptiman A, Zafirelis M. Users Guide to Pitfalls and Lessons Learned About HBOC-201 During Clinical Trials, Expanded Access, and Clinical Use in 1,701 Patients. Shock, 2019; 52(1): 92-99.
26. Rodrigues AD, Ribeiro LR. Blood systems, incompatibilities and alternative procedures to transfusion. Brazilian Journal of Development, 2021; 7(2): 13007-13027.
27. Rifkind JM, Mohanty JG, Nagababu E. The pathophysiology of extracellular hemoglobin associated with enhanced oxidative reactions. Front Physiol, 2015; 5: 500.
28. Vicent JL, Privalle Ct, Singer M, Lorente JA, Boehm E, Meier-Hellmann A et al. Multicenter, randomized, placebo-controlled phase III study of pyridoxalated hemoglobin poloxyethylene in distributive shock (PHOENIX). Crit Care Med, 2015; 43(1): 57-64.
29. Ter-Gazarian. Perftoran: export blood [online]. Russia Beyond, 2014. Available at: https://es.rbth.com/cultura/technologias/2014/10/17/perftoran_sangre_de_exportacion_44415
30. Silverthorn . Human Physiology. An integrated approach. Ed Panamericana, 6th ed., 2014.
31. Van Hemelrijck J, Levien LJ, Veeckman L, Pitman A, Zafireliz Z, Standl T. A safety and efficacy evaluation of hemoglobin-based oxygen carrier HBOC-201 in a randomized, multicenter red blood cell controlled trial in noncardiac sugery patients. anest Analg, 2014; 119(4): 766-76.
32. Thomas, Liji. Components and function of blood plasma [wn line]. News-Medical, 2018. Available at: https://www.newsmedical.net/health/Blood-Plasma-Components-and-Function-(Spanish).aspx.