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Current research on artificial blood

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Abstract
This article gives a summary of the state of the art regarding artificial blood research, emphasizing its biological foundation, primary uses, current state of the art, and obstacles encountered. It also examines the potential of artificial blood in clinical settings by examining the biomechanics, biological characteristics, and physiological roles of blood constituents like plasma, erythrocytes, and platelets. The essay also covers the issues about the preparation and application of artificial blood and suggests the directions for future research.

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Introduction

Plasma and blood cells make up the majority of the blood, which is an opaque crimson liquid that travels through the heart and all blood vessels [4] (as depicted in Figure 1). Many nutrients found in blood cells, including inorganic salts, oxygen, cellular metabolites, active hormones, enzymes, and antibodies, serve to nourish the tissues, control the organ function, and fend against dangerous substances [5]. The amount of blood in an adult weighs 8 to 9% of his/her body weight, approximately 4800 to 5400 ml for a healthy person weighing 60 kg.

Plasma and blood cells make up blood. Venous and arterial blood are two different types of blood. Plasma, blood cells, leukocytes, and platelets are the four parts of blood [6]. Plasma makes up to 55% of these four groups, whereas blood cells and platelets make up up to 45%.

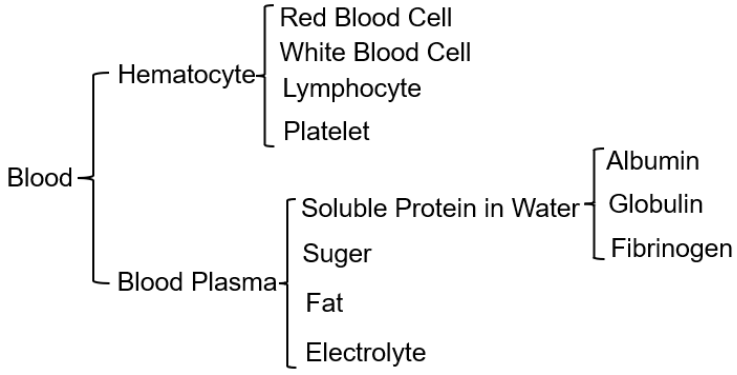

Fig 1: Classification of blood

Blood Function

The blood delivers waste products to the kidneys and distributes oxygen and other vital nutrients to the cells. Red blood cells deliver oxygen, white blood cells stop infection, and platelets stop bleeding; all of these types of cells are created in the bone marrow. Our blood pressure is maintained by plasma, which makes up 55% of the blood. Anemia develops when the amount of hemoglobin in red blood cells is low. Haemoglobin is a protein found in red blood cells that carries oxygen molecules. What steps can be taken to stop bleeding when a blood vessel bleeds? Platelets are related to other blood components and information. Heavy bleeding results from failure in blood clotting mechanism. The body can also remove unwanted clots. Too many clots can block a blood vessel and, depending on the site, result in stroke or heart attack. The delicate balance in the blood is highlighted by the fact that blood malignancies like leukemia develop when healthy white blood cells in the bone marrow are replaced by malignant cells.

All areas of the body, including those that receive oxygen from the lungs and nutrition from the digestive system, depend on the blood for the transportation of nutrients and oxygen. In order to ensure appropriate metabolism, blood can also transport carbon dioxide and other waste products created during the body's metabolic processes to the lungs and kidneys. Red blood cells play a significant role in oxygen transport, although they can be impacted by anemia. The blood is significantly impacted when there is a considerable decline in the quantity and quality of red blood cells, which can result in a number of pathological alterations. Blood also plays crucial physiological roles in fluid management, the stabilization of the internal environment, the strengthening of immunity, and thermoregulation.

Why artificial blood is needed?

In recent years, the scarcity of blood supply all over the world has triggered widespread social concern [7-9]. Despite the government's active promotion of gratuitous blood donation, due to the tight supply there is still an imbalance between supply and demand even though the number of times of gratuitous blood donations and the volume of blood collected have been continuously increasing over the past 20 years [10, 11]. According to the World Health Organisation, 117.4 billion units of blood are donated globally every year, but this amount is still far from enough to meet the demand for clinical usage [12, 13].

With the advancement of science and technology, the traditional blood transfusion method can no longer meet the needs of today's society because of the difficulties in storage and transport, potential risk of viral infection, confusion of blood types, and lack of special blood types. Therefore, the development of an artificial blood that is both portable and safe has become an important means of managing blood shortages and preventing transfusion-transmitted diseases today [14], as well as a necessity for wartime medical treatment.

What is artificial blood?

Artificial blood, also known as artificial replacement blood, is a blood substitute made through the use of specific drugs or materials [15, 16]. These usually include drugs that provide oxygen, protect the acid-base balance inside blood vessels and increase blood flow. These drugs are usually made from natural materials (e.g., dextran, gelatin, glucose, hydroxyethyl starch, etc.), organic chemical materials (e.g., polymeric umbrella fluorocarbons), and drugs manufactured using biological methods.

Human blood components include white blood cells, red blood cells, platelets, as well as a large number of electrolytes, proteins, etc. The current artificial blood is only a product with certain blood functions, of which haemoglobin and red blood cells capable of carrying oxygen and carbon dioxide are the primary concern.

Current Research for Artificial Blood

Perfluorocarbon

Perfluorocarbons (PFCs) are colourless, stable liquids. In the 1960s, researchers [17] discovered by chance that PFCs had the ability to carry oxygen which is even better than that of the normal blood. This discovery started the journey of using PFCs as the blood substitute.

In 1946 Bruk proposed the use of cobalt histidine compounds as the artificial blood. In 1966, Clark discovered [18] that perfluorochemicals (Perfluoro chemical hereinafter referred to as PEC) has excellent capability in carrying oxygen. In 1967, Sloviter *et al*. [19] performed cerebral perfusion in rats using albumin stabilisers. In 1968, Geyer *et al*. implemented blood exchange using perfluorotriamine emulsions and showed that rats could be adequately nourished within 8h. Clark's animal experiments achieved satisfactory success in cardiac perfusion.

In 1970, Kohno and others accomplished 90 per cent blood replacement using fluorocarbons and were able to maintain viability for an extended period of time through an experiment on a dog. This marked the first attempt to transfer a natural resource into the human body, and Kohno and the Green Cross Central Research Institute in Japan continued their research for 11 years after that. Initially, the perfluorocarbon emulsion proved to have good carbon dioxide adsorption and elimination properties, and it also helped maintain the long-term life of isolated organs. Subsequently, scientists began to conduct more in-depth research on this emulsion in order to minimise its adverse effects, and in 1979, a perfluorocarbon emulsion was first used in single-kidney transplants in Japan. 1980, scientists from the Shanghai Institute of Organic Chemistry and the Third Military Medical University worked together for five years to develop artificial blood, which was made from fluorocarbons as the main ingredient, forming the basis for a new form of artificial blood. The main ingredient is fluorocarbon compounds, forming a special emulsion with a yellowish colour, which can be absorbed by the human body like red blood cells, and can also effectively release a large amount of carbon dioxide. Regardless of one's origin, healthy blood can be obtained from these bodies with good biological and chemical characteristics.

In recent decades, many professionals and technicians have devoted themselves to the development of various blood products, including stock solutions, suspensions, solutions, etc., with the aim of achieving more economical and efficient blood utilisation. In addition, they have developed a variety of alternative stock solutions, such as dextran, gelatin, hydroxyethyl starch, etc., which have been widely used. These colloidal solvents can effectively increase the concentration of plasma, however, they are unable to achieve a true organic combination of blood and air

After many clinical trials, it was confirmed that despite its high oxygen carrying capacity, PFCs could not provide

nutrients, could not coagulate blood, and lacked important immunity against infections, so most PFC man-made products ended in failure.

Synthetic haemoglobin

In order to solve this problem, people began to study haemoglobin, which is one of the most important components of blood function in the human body. Haemoglobin is the basis of human life [20] and it is not only derived from humans but also from other animals [21, 22].

"Pure Blood" is an American bovine-derived haemoglobin preparation that has been evaluated in more than 20 clinical trials with 800 users, and experiments have shown that it can be used safely and reliably for up to three years, has good compatibility with a wide range of blood types, and carries oxygen far more efficiently than ordinary blood. "Pure Blood" has significant side effects, which are 5 per cent more severe than those of blood. Although the United States Food and Drug Administration (FDA) has suspended the use of "pure blood" due to considerations about these side-effects, it is allowed to be used in some clinical practices such as treatment of autoimmune haemolytic anaemia.

In 2013, Romanian scientists invented a new type of blood, which is extracted from a variety of substances such as water, inorganic salts, earthworm haemoglobin, etc., which not only has the properties of blood, but also facilitates rapid oxygen and carbon dioxide transport. In December of the same year, Japanese researchers also made an important breakthrough by separating red blood cells and obtaining more of them, which effectively reduced the pressure on the blood supply.

In 2021, the research team of Northwestern University [23] developed a human blood product known as "artificial universal blood" over a period of 20 years. It can cross the boundary of blood type, without the need for matching, and can be used according to the need, and covers almost all the blood types, such as Rh-negative. The product has been well tested in animal models and is supported to enter phase I clinical research. It is expected that this artificial blood used as the "breakthrough therapeutics" will greatly improve the clinical practice and greatly relieve the tension in blood supply. Research has also demonstrated that haemoglobin, a synthetic oxygen carrier, needs to take into account the blood's oxygen affinity and half-life at the same time. The discovery of biocompatible materials represents another novel avenue for the future.

Stem cells

In the exploration of human haematopoiesis, the "all-powerful" stem cells have naturally not been overlooked by researchers. Researchers have shown that stem cells are highly therapeutic, and the use of haematopoietic stem cells to treat human diseases has become a popular topic in life and health research today. From an immunological and physiological point of view, blood cultured from haematopoietic stem cells can be used as an alternative to natural blood, as they are identical to the "original" blood and can better meet the physiological needs of the human body.

In 2011, Giarratana [24] *et al*. succeeded in using pluripotent stem cells to induce the generation of erythrocytes, which were fed into the human body, thus enabling the effective delivery of artificial blood, a discovery that has brought about a major breakthrough in human health, but more is needed in order to achieve large-scale application of this product.

In 2016, scientists at Washington University in St. Louis invented soluble blood, which is a completely new form of blood. It has an ice cube-like shape, can be easily absorbed without solvents, and has an ultra-long storage period. However, the product has not been tested through animal experiments and clinical trials. Yan *et al*. [25] finally researched the preparation method of "artificial plasma" while artificial red blood cells were perfectly accomplished by using the dried bacteria method.

Advantages and disadvantages of artificial blood

Artificial blood, like other medicines, can be used in operating theatres, emergency rooms, wards, etc. to cope with emergency needs; because of the absence of blood grouping substances, there is no need to check the blood group and cross-testing, which is suitable for first aid; because of the absence of pathogens, there is no need to worry about infections due to blood transfusion; it can be used immediately for patients with rare blood groups, which saves the effort in determining the type of blood; and it can be used by patients who refuses to have transfusions due to religious reasons. The disadvantage is that the oxygen transport function of artificial blood is very low compared to haemoglobin, and there are acute or chronic side effects and complications, the accumulation of its toxicity in the reticuloendothelial system of the body, for which more experience has yet to be gained.

The Biomedical Basis of Artificial Blood

Classification of artificial blood

According to its main components and functions, artificial blood can be divided into whole blood type artificial blood, plasma type artificial blood and platelet type artificial blood. Whole blood-type artificial blood contains all the components of whole blood and can completely replace natural blood; plasma-type artificial blood mainly simulates the components of plasma and can be used to replenish blood volume; platelet-type artificial blood is mainly used to simulate the function of platelets and accelerate blood clotting.

Biophysical properties of artificial blood

The biophysics of blood includes viscoelasticity, permeability, and fluidity, which are important properties for maintaining blood circulation as well as organ function in the human body. Modelling these properties is one of the key challenges in the study of artificial blood.

Summary

Current research is focused on developing new types of artificial blood with superior properties. For example, researchers are trying to modify cells, iron-based nanoparticles, or microorganisms [26] using genetic engineering techniques to produce specific artificial blood components, while others [27-30] are exploring the use of biomaterials to mimic the physicochemical properties of blood.

Storage and transport are other important aspects of artificial blood application. How to ensure the effectiveness of artificial blood while achieving its long-term storage and convenient transport is a challenging problem.

Although there have been many studies on artificial blood that have achieved remarkable results, there are still many challenges that need to be addressed. For example, how to ensure the safety of artificial blood, how to ensure that it has

the same biological activity in vivo as natural blood, and how to improve its production efficiency and reduce costs. Future research should focus on these challenges, but also on the need for a deeper understanding of the biological properties and physiological functions of blood in order to develop more efficient and safer artificial blood. Overall, although there are many challenges to overcome, the possibility of artificial blood replacing natural blood is gradually increasing as technology advances.

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