Advancements in Synthetic Blood Components

Introduction:

In the words of one of the greatest intellectual minds of the 16th century, "Blood is a very special juice" (Goethe). He isn't wrong. Blood is one of the most valuable substances in the world at hundreds of dollars per liter. There have been several attempts at creating viable synthetic alternatives in place of this life-giving elixir, some dating as far back as the 1600s. According to the N.I.H., (National Institute of Health) since 1616 when it was discovered how blood circulated through the body, everything under the sun including alcohol, milk, urine, plant residue, and cattle blood has been used as a substitute. Unsurprisingly, after many patients had reactions and died because of treatment, none of these were found to be a suitable substitute for real blood. Later in the late 1800s, it was discovered that a solution of sodium, potassium, chloride, and later lactate, named Ringer's solution, kept the heart beating during a hemorrhage. Although this was not a blood substitute, this solution is still used today to replace blood volume in the circulatory system. Later still, more understanding of blood groups, other blood antigens, and pH continued to make blood transfusions safer and more effective.[1]

The world has learned much about transfusion medicine since the 1600s, but even with that knowledge, we have yet to come up with a suitable substitute that is free of risk and readily available at a moment's notice. However, with today's technology, it is possible that within our lifetime we could see an alternative source of blood that is cheap to manufacture, always available, free of disease, and has a low risk of adverse reactions. This is an exciting time for the

[1] Sarkar, S. (2008, July). *Artificial Blood*. Indian journal of critical care medicine : peer-reviewed, official publication of Indian Society of Critical Care Medicine. Retrieved March 28, 2023, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2738310/

discussion of synthetic blood components as researchers make steady progress toward laboratory-grown blood, artificial platelets, and even cancer-fighting artificial blood components.

Discussion:

In 2022, researchers at Cambridge University began conducting the world's first human trials on laboratory-grown blood cells that have been successfully transfused into patients through the RESTORE project. The blood is derived from pluripotent stem cell populations and is coerced into becoming RBCs through chemical signals called cytokines. Since this is blood grown in a lab, these cells promise to last longer than those of donors simply because they are fresher. This seems like a simple way to get blood products, but it is a lot harder in practice than in theory. Right now, it is extremely labor-intensive and expensive to produce even a small amount of these cells. The trials conducted so far have only seen one to two teaspoons of blood transfused into patients.[2] It does not seem very promising if you are hemorrhaging or need blood consistently. The average transfusion is around one hundred times that amount. In the next several years, the project, along with the United Kingdom's National Health Service, plans to work through strategies for scaling up the project to not only make this a safe and cost-effective option but meet the ever-growing demand for blood as well.

While a lot of the spotlight is put on red blood cells, other aspects of transfusion medicine are just as important and, in many aspects, harder to manage. The greatest advancements in blood components to date have not been in red blood cells but in platelets. A substantial portion of these platelets are used in trauma events. Whereas someone with a chronic disease or platelet disorder may need one or two bags of platelets, people in trauma situations can use several units

[2] *First ever clinical trial of lab-grown red blood cell transfusion*. University of Cambridge. (2023, March 24). Retrieved March 28, 2023, from https://www.cam.ac.uk/research/news/first-ever-clinical-trial-underway-of-laboratory-grown-red-b

of platelets in no time at all. Not to mention, platelets are the hardest blood component to work with. They have a short shelf life of about seven days, and they are easily contaminated with bacteria due to their room-temperature storage requirements. Platelets are like your pet beta fish you got when you were younger. They are needy, and they always seem to die about a week after you get them. Scientists, such as Anirban Sen Gupta, Ph.D., have been working diligently on how to make your fish – I mean… your platelets not only live longer but address problems concerning availability, stability, and more. These are not your Average Joe brand of platelets; they are synthetic and can be manufactured outside the body.

Dr. Gupta, a biomedical engineer at Case Western Reserve University, and his team have helped develop liposome-based platelet-mimicking procoagulant nanoparticles (PPNs). These PPNs promise to do the job of platelets while being safer and more reliable than their all-natural counterparts for the reasons stated above. Imagine not having to worry as much about bacterial contamination because you do not have to introduce skin bacteria into the system. Imagine being able to manufacture large amounts of these Frankenstein platelets around the clock and not have to rely on the kindness of donors to be the sole supplier of platelets in the world. This all sounds great, but do they work? In small-scale animal trials, the answer is yes. These PPNs can mimic two important aspects of natural platelets by not only being able to sense that there is a bleed but also having the ability to activate the formation of fibrinogen to fibrin and form a platelet plug.[3] In this study, rats were used to test the platelets' ability to clot in a traumatic hemorrhage situation. The rats had about thirty percent of their liver removed and were sown up with gauze placed inside the abdomen. The control group was injected with saline while the other was injected with PPNs. One hour after the procedure, the gauze was removed, weighed, and it was

[3] Scott, M. (2022, February 1). *Stopping heavy bleeding with next-generation artificial platelets*. The Daily. Retrieved March 28, 2023, from https://thedaily.case.edu/stopping-heavy-bleeding-with-improved-artificial-platelets/

found that there was a fifty percent reduction in bleeding time in rats injected with PPNs versus those injected with saline.[4] This shows at least in small, controlled studies, PPNs can serve as a viable substitute for platelets.

This works great for people who need to stop bleeding fast, but another large consumer of blood products are those with chronic diseases such as cancer. Cancer treatment often involves chemotherapy and radiation which stops cancer from dividing and spreading, but it also stops your cells from dividing which means a lot of people need blood products consistently. There is a little-known fact about platelets that might just help people to need fewer transfusions overall but also help actively treat cancer. These rogue cancer cells have come up with some mission-impossible invasion tactics to avoid detection by the body. It just so happens that many of these cells have an affinity for platelets. They use these interactions with platelets to not only hitch a ride around the body but also to coat themselves with platelet membranes and avoid immune detection. According to Michael R. King, a biomedical engineer at Cornell, a major interaction that makes this possible is that membrane proteins such as P-selectin bind to CD44 on many cancer cells. King and many scientists like him have discovered ways to use these interactions to their advantage by coating synthetic platelets with cancer drugs such as TRAIL and doxorubicin that make cells apoptotic. Not only do they specifically target cancer cells, but like a heat-seeking missile, they can circulate in the body to find other cancer cells to destroy. Many other applications are being tested with platelet-drug interactions such as antibiotic drug attachments to treat bacterial sepsis.[5] The same steps are being taken with fully synthetic red blood cells.

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[4] Singh Sekhon, U. D., Swingle, K., & Girish, A. (2022, January 26). *Platelet-mimicking procoagulant nanoparticles augment hemostasis in animal models of bleeding*. Science Translocational Medicine. Retrieved March 28, 2023, from https://www.science.org/doi/10.1126/scitranslmed.abb8975

[5] Arnaud, C. H. (2016, January 16). *How Platelet Disguises Could Aid Drug Delivery*. Cen.acs.org. Retrieved March 28, 2023, from https://cen.acs.org/articles/94/i3/Platelet-Disguises-Aid-Drug-Delivery.html

Researchers Wei Zhu and Jeffery Brinker have even devised a way to have these cells detect certain bacterial toxins but also act as decoys for them.[6] While these applications are not directly associated with transfusions for the sake of increasing cell lines or to completely get rid of the donor as a source of blood products, if these treatments can be proven successful, there would be far fewer people needing blood products altogether. This would free up supply and allow for synthetic products to enter the market at a slower pace where they might be considered a viable alternative.

Conclusion:

As mentioned before, there have been several attempts to create synthetic blood products dating back to the 1600s by injecting milk, and alcohol, among other things into humans, to now in the 21st century using stem cells and biodegradable molds to mimic the properties of human cells. So far, in today's world where we have mastered leaving our planet and going to space, transplanting a dead person's heart to another human and making it beat again, and the ability to become rich and famous by posting dancing videos on TikTok, we have still yet to master the creation of synthetic blood that works just as well as what our body can already create on its own. There are tens if not hundreds of research projects that are going on simultaneously with the same goal to create a world where we don't have to rely on donors to be the sole supplier of blood in the world, and where we can have safe, effective transfusions without the risk of reactions or disease. Some of the projects discussed could be transformative for transfusion medicine and the world, but only time will tell. For the time being, blood will remain a very special juice for millions, whose only hope of survival is the kindness of donors like you and me.

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[6] *Synthetic red blood cells mimic natural ones, and have new abilities*. American Chemical Society. (2020, June 3). Retrieved March 28, 2023, from https://www.acs.org/pressroom/presspacs/2020/acs-presspac-june-3-2020/synthetic-red-blood-cells-mimic-natural-ones-and-have-new-abilities.html