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Red blood cell replacement, or nanobiotherapeutics with enhanced red blood cell functions?

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Abstract

Why is this important?

Under normal circumstances, donor blood is the best replacement for blood. However, there are exceptions:

- **During natural epidemics (e.g., HIV, Ebola, etc.) or man-made epidemics (terrorism, war, etc.), there is a risk of donor blood being contaminated, and donors being disqualified because they have contracted disease. Unlike red blood cells (RBCs), blood substitutes can be sterilized to remove infective agents.**
- **Heart attack and stroke are usually caused by obstruction of arterial blood vessels. Unlike RBCs, which are particulate, blood substitutes are in the form of a solution that can perfuse through obstructed vessels with greater ease to reach the heart and brain, as has been demonstrated in animal studies.**
- **Severe blood loss from injuries sustained during accidents, disasters, or war may require urgent blood transfusion that cannot wait for transportation to the hospital for blood group testing. Unlike RBCs, blood substitutes do not have specific blood groups, and can be administered on the spot.**
- **RBCs have to be stored under refrigeration for up to 42 days, and are thus difficult to transport and store in times of disaster and at the battlefront. Blood substitutes can be stored at room temperature for more than 1 year, compared to the RBC shelf life of 1 day, at room temperature.**
- **In cases of very severe hemorrhagic shock, there is usually a safety window of 60 min for blood replacement, beyond which there could be problems related to irreversible shock. Animal studies show that a particular type of blood substitute, with enhanced RBC enzymes, may be able to prolong the duration of the safety window.**

Keywords: donor blood, blood substitiute, oxygen carrier, antioxidant, carbon dioxide transport, hemoglobin, catalase, superoxide dismutase, carbonic anhydrase, irreversible hemorrhagic shock

What is the present status around the world?

The first report of artificial cells includes artificial RBCs (Chang 1964, Chang and Poznansky 1968, Chang 1971a) (with support from MRC Canada). It was commonly believed that a blood substitute was a simple matter that could be quickly developed when needed. Thus, research on blood substitutes was put aside, and only the other areas pertaining to artificial cells were extensively developed for widespread use around the world (Chang 2005, Orive et al. 2003, Chang 2007). When the AIDS epidemic struck in 1989, there were no blood substitutes available, and many patients were infected with HIV-contaminated donor blood. It was only then that intense R&D on blood substitutes was belatedly carried out around the world. It was realized too late that the development of a blood substitute requires the same long-term research as for any other medical research on cancer and other diseases. Thus, the present status is only as follows (Przybelski et al. 1996, Tsuchida 1998, Klein 2000, Kobayashi et al. 2005, Winslow 2006, Zuck 2006, Liu and Xiu 2008, Mozzarelli and Bettati 2011, Zapol 2011, Yang et al. 2013, Chang 2013, Kim and Greenburg 2014, Weiskopf 2014):

RBCs have three major functions: (1) transport of oxygen from the lung to the tissue, (2) removal of damaging oxygen radicals, and (3) transport of carbon dioxide (CO_2) from the tissue to the lung, to be excreted through exhalation.

1. Hemoglobin-based oxygen carriers (HBOCs): It is thus not surprising that after more than 20 years of R&D around the world, only oxygen carriers have been tested clinically. The most extensive clinical trials were based on polyhemoglobin (PolyHb) developed independently, mainly by two groups (Northfield—on human PolyHb, and BioPure—on bovine PolyHb), using the basic principle of glutaraldehyde-cross-linked hemoglobin that was first reported by Chang (1971b). This does not contain into any blood groups, can be pasteurized to remove infective agents, and can

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be stored at room temperature for more than 1 year. Large-scale clinical trials have been carried out (Gould et al. 2002, Jahr et al. 2008), including emergency use in the ambulance, without the need for typing or cross-matching (Moore et al. 2009). Oxygen carriers are commonly called "oxygen therapeutics". For some conditions, in addition to oxygen, the other two RBC functions may also be required: the removal of harmful oxygen radicals, and the transport of CO_2.

2. Transport of oxygen and the removal of oxygen radicals: This can be a soluble complex of PolyHb containing antioxidant enzymes to remove oxygen radicals (PolyHb–SOD–CAT) (D'Agnillo and Chang 1998). It can prevent ischemia/reperfusion injury in the case of hemorrhagic shock/cerebral ischemia (Powanda and Chang 2002) (with support from CIHR and FRSQ). Conjugated hemoglobin containing synthetic antioxidants (PNPH) (Ma and Hsia 2013) is another example. Other examples include those of Simoni et al. (1997), Rousselot et al. (2006), Jia and Alayash (2013).
3. All three RBC functions (transport of oxygen, removal of oxygen radicals, and transport of CO_2): Other conditions, such as in sustained severe hemorrhagic shock, may require all three RBC functions. With support from the CIHR/Canadian Blood Service, we have designed a novel soluble nanobiotechnological complex (PolyHb–SOD–CAT–CA). In this complex, not only are all three RBC functions present, they are also enhanced due to the increased concentrations of RBC enzymes in the complex. These RBC enzymes can be extracted from RBCs inexpensively (Guo et al. 2015). This complex does not contain into any blood groups. The lyophilized preparation can be heat-pasteurized at 68F for 2 h. This can be important if there is a need to inactivate the HIV virus, Ebola virus, and other infective organisms. Unlike the storage time of about 1 day for RBCs at room temperature, this lyophilized preparation can be stored at room temperature for 320 days. The results we obtained using an animal model of 90-min hemorrhagic shock with a 2/3 loss in blood volume shows that it is superior to whole blood, which was determined by observing the following parameters: lowering of elevated intracellular pCO_2, recovery of ST elevation, troponin levels, lowering of elevated lactate, and histology of the heart and intestine. More details can be accessed from the full text of Bian and Chang (2015) freely available online at http://informahealthcare.com/doi/pdf/10.3109/21691401.2014.964554.

To date, progress in research conducted worldwide shows that it is possible to produce tailor-made blood substitutes, ranging from simple to complex preparations. It is imperative that these should be actively developed for clinical use without waiting until it is too late again. We need to analyze the specific indications for 1, 2, and 3 above. If a condition only requires the administration of oxygen, then there is no need to use a more complex preparation. On the other hand, it would be a folly not to use a more complex substitute if indicated. We also need to intensify research on the many important ongoing developments around the world (Bian et al. 2011, Buehler et al. 2004,Gould et al. 1995, Hoffman et al. 1990, Natanson et al. 2008, Seetharama et al. 2013, Sims et al. 2001, Tam et al. 1976, Wei et al. 2013, Yabuki et al. 1990, Yu et al. 2010, Zhu et al. 2007, Zhou et,al. 2013, Lui and Kluger 2010, Wong and Chang 2007, Bucci 2011, Chang 1957, Greenburg 2013, Sakai 2013, Wong 1988). Examples include: develop other novel approaches including novel crosslinkers; new sources of material from porcine, bovine, and human cord RBC, recombinant Arenicola marina; basic research on nitric oxide, oxidative stress, haptoglobin, rate of oxygen supply, safety and efficacy analysis, and many other areas. The 2015 XV International Symposium on Blood Substitute, at Lund University (Professor Lief Bulow), Lund, Sweden, (http://isbs2015.lu.se), to be followed by the 2017 XVI symposium at McGill University (Professor TMS Chang), Montreal, Canada (www.medicine.mcgill.ca/artcell), will be excellent opportunities for international exchanges.

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Declaration of interest

The author reports no declaration of interest. The author alone is responsible for the content and writing of the paper.

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