Haemoglobin-Based O_2 Carriers Designed for Use as a Red Blood Cell Substitute

*Teruyuki Komatsu**

Department of Applied Chemistry, Faculty of Science and Engineering, Chuo University
1-13-27 Kasuga, Bunkyo-ku, Tokyo 112-8551, Japan
komatsu@kc.chuo-u.ac.jp

Modern medicine requires an adequate blood supply for transfusion. Nevertheless, declining birth rate and aging population are reducing the number of blood donors, resulting in a shortage of blood worldwide. In particular, red blood cell (RBC) substitute is necessary for a medical measure to compliment transfusion therapy. In the last few decades, haemoglobin (Hb)-based O_2 carriers (HBOCs) of several kinds have been developed as RBC alternatives.[1] However, none has been assigned yet for practical use because of several concerns.

We have recently synthesized various HBOCs and have evaluated their O_2 binding properties, safety, and efficacy. First, Hb was wrapped covalently with human serum albumins (HSAs), yielding Hb-HSA_3 cluster.[2,3] The AFM observation and 3D reconstruction based on cryo-TEM images revealed a triangular structure.[2,4] Hb-HSA_3 showed higher O_2-affinity than that of native Hb.[5] Various clusters containing a recombinant Hb mutant core which possesses different O_2 affinities have also been created.[6,7] Intravenous administration of Hb-HSA_3 into anesthetized rats did not elicit unfavourable side-effects, such as an increase in systemic blood pressure.[8] Physiological responses to the transfusion in acute anaemia rat model (50% blood withdrawal) demonstrated that Hb-HSA_3 has an ability to resuscitate the haemorrhagic shock.[9] These results suggest that the Hb-HSA_3 solution can be of medical importance for alternative material of RBC transfusion.

Second, we prepared core-shell structured Hb nanoparticle (HbNP).[10] Covalently binding of HSA to sphere composed of polymerized Hbs yielded HbNP. The diameter was ascertained as approximately 90 nm by SEM. The similar particle made of stroma-free Hb (SFHb) containing natural antioxidant enzyme catalase (SFHbNP) formed a very stable O_2 complex even in aqueous H_2O_2 solution. The SFHbNP possessed good blood compatibility and did not affect the functionalities of the blood cell components.

Polyethylene glycol (PEG)-conjugated Hbs have been widely developed.[11] Nonetheless, administration of PEG-conjugated proteins has been recently shown that anti-PEG antibodies generate in the body. Poly(2-ethyl-2-oxazoline) (POx) is a potential alternative for PEG. Third, we prepared POx-conjugated Hbs (POx-Hb) for both human and veterinary use.[12]

References:

[1] Gupta, A. S. *Shock* **2019**, *52*, 70−83.
[2] Tomita, D.; Komatsu, T. et al., *Biomacromolecules* **2013**, *14*, 1816–1825.
[3] Funaki, R.; Komatsu, T. et al., *ACS Omega* **2019**, *4*, 3228–3233.
[4] Shinohara, R.; Komatsu, T. et al., *J. Phys. Chem. Lett.* **2017**, *8*, 819–824.
[5] Morita, Y.; Komatsu, T. et al., *J. Phys. Chem. B* **2018**, *122*, 12031–12039.
[6] Funaki, R.; Komatsu, T. et al., *J. Mater. Chem. B* **2020**, *8*, 1139–1145.
[7] Morita, Y.; Komatsu, T. et al., *Chem. Commun.* **2021**, *57*, 9144–9147.
[8] Iwasaki, H.; Komatsu, T. et al., *Art. Cells Nanomed. Bitechnol.* **2018**, *46*, S621–S629.
[9] Okamoto, W.; Komatsu, T. et al., *J. Biomed. Mater. Res.* **2022**, *110*, 1827–1838.
[10] Okamoto, W.; Komatsu, T. et al., *ACS Appl. Bio Mater.* **2022**, *5*, 5844–5853.
[11] Portörő, I. et al., *Biochim. Biophys. Acta* **2008**, *1784*, 1402–1409.
[12] Okamoto, W.; Komatsu, T. et al., **2023**, submitted.