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Multifunctional Synthetic Mimics of Red Blood Cells

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The timely administration of donor red blood cells (RBCs) is crucial to improve survival following acute bleeding resulting from e.g., a traumatic injury. However, the use of donor RBCs prior to hospital admission is hampered due to their limited availability and portability, special storage requirements, the need for blood type matching due to the RBCs membrane antigens and the risks for disease transmission. Hence, a great effort is currently being devoted to developing RBCs substitutes that could be used as a "bridge" to maintain tissue oxygenation until hospital admission.

While haemoglobin (Hb) has evolved to have excellent oxygen transporting properties, when outside the protective environment of RBCs, the Hb tetramer breaks down promoting severe adverse effects. Thus, in recent years, several strategies for encapsulating Hb have been explored. However, despite the tremendous progress achieved, it is still a challenge to entrap Hb within a well-defined structure preserving its secondary structure while allowing for the diffusion of oxygen in and out of the system. Additionally, the auto-oxidation of Hb into non-functional metHb together with the difficulties in achieving long circulation times in vivo are two important aspects that are currently hampering the HBOCs translation into the clinic.

In this context, we have successfully encapsulated Hb within a type of metal–organic framework (MOF)-based nanoparticles (NPs). MOF-NPs have unique advantages due to their large surface areas and well-defined crystalline porous structures. Specifically, we have employed the porous coordination network (PCN)-333 which displays one of the largest void volumes allowing for a high Hb loading and one of the largest cages.[1] The later permits the encapsulation of individual Hb molecules within predefined cavities, thus preventing misfolding or denaturation.

While within native RBCs metHb conversion is prevented by a set of antioxidant enzymes, our RBCs substitutes make use of antioxidant nanozymes (NZs). NZs, which are nanomaterials with catalytic properties, display high stability and can potentially be prepared at large scale at a reasonable cost. Specifically, we have incorporated cerium oxide-, gold-NPs and gold nanoclusters as NZs and demonstrated that they are able to catalytically deplete prominent reactive oxygen species and minimize Hb's oxidation into metHb.[2]

Finally, since an ever-present concern for successful RBCs substitutes is to achieve long circulation in the bloodstream, we have developed stealth coatings which include PEG but also decoration with membranes extracted from native RBCs, which are able to remain in circulation for up to 120 days.

1. Liu, X.; Jansman, M. M. T.; Hosta-Rigau, L. *Haemoglobin-Loaded Metal Organic Framework Based Nanoparticles Camouflaged with a Red Blood Cell Membrane as Potential Oxygen Delivery Systems*. **Biomaterials Science**, 2020, 8, 5859.
2. Jansman, M. M. T.; Liu, X.; Kempen, P.; Clergeaud, G.; Andresen, T. L.; Thulstrup, P. W.; Hosta-Rigau, L. *Hemoglobin-Based Oxygen Carriers Incorporating Nanozymes for the Depletion of Reactive Oxygen Species*. **ACS Applied Materials and Interfaces**, 2020, 12, 50275