Redox responsive manganese-based MRI theranostics for cancer therapy

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Smart theranostics are dynamic platforms that integrate multiple functions, including at least imaging, therapy and responsiveness, in a single agent. [1, 2]. This work focuses on the synthesis, characterisation and evaluation of manganese dioxide (MnO_2)-based redox responsive magnetic resonance (MR) nanotheranostics for cancer therapy. These systems feature a Pt(IV) complex as a chemotherapy prodrug, bound to MnO_2 nanoparticles. In the presence of reducing agents (e.g. glutathione), the Pt(IV) complex is reduced, thus releasing the active drug cisplatin. The same agents also reduce the MnO_2 particles to Mn(II), inducing an OFF-ON T_1 MR signal switch (Figure 1A).

Using facile ultrasonication reactions [3], we investigated a series of Mn_xO_y-Pt(IV) samples in regards to their performance as redox-responsive MR contrast agents. Relaxometry studies performed at 1.47 T revealed signal enhancements as high as 136-fold for nanoparticles with lower Pt/Mn ratios after treatment with a reducing agent, in agreement with the MRI contrast enhancement observed in phantom images acquired at clinical fields of 3T (Figure 1B). Cell cytotoxicity was also assessed in a lung carcinoma (A549) cell line in order to study the therapeutic effect of the developed conjugates (Figure 1C). Results in 2D cultured cells show a lower toxicity for the MnO_2-Pt(IV) nanosystem (IC_{50} = 100.0 µM) when compared to that of cisplatin (IC_{50} = 31.6 µM), but considerably higher toxicity than that of a Pt(IV) prodrug (IC_{50} = 420.5 µM). This highlights a dual therapeutic effect where the Mn(II) species play a key role. Further cell studies point to the participation of the free Mn(II) ions released from the nanoparticles in Fenton-like reactions, leading to the activation of ferroptosis in addition to apoptosis (by cisplatin). Ongoing *in vitro* studies in 3D A549 cell cultures aim to explore the imaging and therapeutic efficiency of these MnO_2-Pt(IV) nanoparticles in a more representative tumour microenvironment.

REFERENCES

[1] A. Parodi, M. Rudzinska, S. Leporatti, Y. Anissimov and A. A. Zamyatnin Jr, Front Bioeng Biotechnol, 2020, 8, 503.
[2] M. E. Caldorera-Moore, W. B. Liechty and N. A. Peppas, Acc Chem Res, 2011, 44, 1061-1070.
[3] M. Bañobre-López, L. García-Hevia, M. F. Cerqueira, F. Rivadulla and J. Gallo, Chem Eur J, 2018, 24, 1295-1303

FIGURES

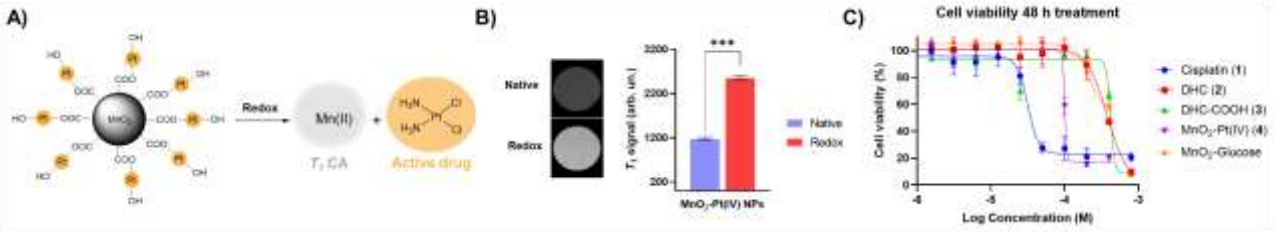

Figure 1: A) Schematic representation of the reduction MnO_2 nanoparticles by reducing agents. B) T_1-weighted MRI phantoms images for MnO_2-Pt(IV) nanoparticles and corresponding signal shift with addition of AA (10 mM), [Mn] = 0.2 mM, ***p<0.0001. C) Cell viability of A549 cells after 48 h of treatments (n=3). Concentration refers to Pt concentration for all treatments except for MnO_2-Glucose, in which the Mn concentration is presented.