Intranasal Administration of Pt(IV) nanoparticles for Glioblastoma treatment

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The progressive population aging in developed countries has favored a steady prevalence increase over the years of many pathologies of the central nervous system (CNS), such as neurodegenerative diseases (e.g., amyotrophic lateral sclerosis, Alzheimer's, Parkinson's, Huntington's, and prion diseases), genetic deficiencies (e.g., lysosomal storage diseases, leukodystrophy) and brain cancer (i.e. glioblastoma multiforme).

Most of neurological diseases (ND) clearly diverge in their origin, overall population incidence and treatment though all of them share the same problem, namely the lack of efficacy of their state-of-the-art therapies originated largely by the existence of the blood-brain barrier (BBB). This barrier limits the access of most therapeutic agents to the brain area, and for those crossing requires ever-increasing drug doses increasing side effects. More specifically, current therapies for treating GB, and brain tumors in general, are inefficient and represent numerous challenges and treated patients face dismal prognosis with a median survival below 15-18 months.

Intranasal administration represents an alternative route to transport drugs from the nasal mucous membrane through the trigeminal nerve, and from there to the brain while largely avoiding the systemic dispersal of the drug and the limitations of BBB. However, as far as we know no IN products for GB are nowadays commercialized mostly due to the poor mucosa penetration of most drugs, the rapid mucociliary clearance and the enzymatic degradation. In this sense, the use of nanotechnology-based approaches is of special interest as allows for control of the formulation, surface charge, hydrophilicity, and mucoadhesion and favors the transcellular transport to the brain as well as induce both a systemic and local immune response. It also allows for the use of effective chemotherapies against GB, such is the case of Platinum (Pt) complexes. So far, and despite the multiple benefits reported in the literature, the administration of Pt complexes is often associated with severe systemic toxicity resulting from long-term treatment. BBB produces scarce drug arrival to the brain when administered orally or intravenously.

To circumvent these limitations, our group has recently reported neuromelanin bioinspired coordination polymer nanoparticles containing Pt (IV) prodrugs as building blocks. This nanoformulation has showed dual pH and redox sensitivity in vitro, showing controlled release and comparable cytotoxicity to cisplatin against HeLa and GL261 GB cells. In vivo intranasal administration in orthotopic preclinical GL261 GB-bearing mice demonstrated increased accumulation of platinum in tumors, leading in certain cases to cure and prolong survival of the tested cohort. For comparison purposes we will also show the activity of the monomeric Pt(IV) complexes as well as other nanoparticles obtained by melanization reactions.

References

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Figures

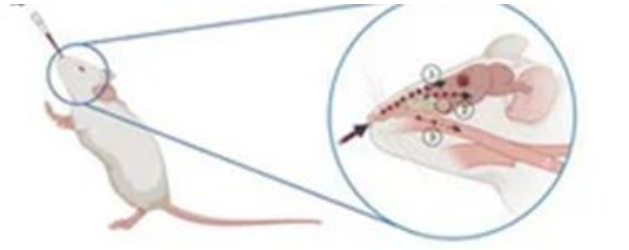

Figure 1. Schematic representation of the intranasal delivery of nanocarriers for Glioblastoma treatment

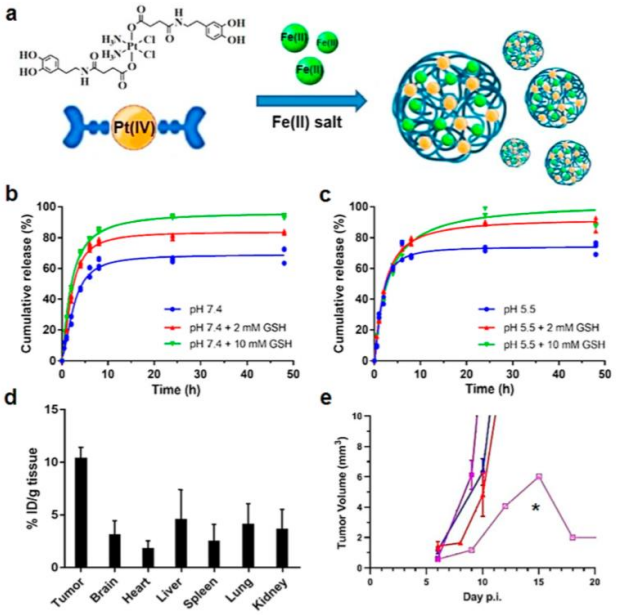

Figure 2. (a) Scheme of the Pt-Fe NCPs synthesis upon polymerization of a Pt(IV) prodrug with iron ions as metal nodes; Cumulative release profiles of Pt from Pt-Fe NCPs at 37 ◦C at (b) pH 7.4 and (c) pH 5.5 in PBS using the dialysis method in the absence or in the presence of glutathione (GSH); (d) Biodistribution of Pt-Fe NCPs in mice organs 1 h after administration (dosage of 1.5 mg/kg, n = 3); (e) Tumour volume evolution in the period 0–20 days post-implantation (p.i.) [blue: control; red: therapy starting point at day 10 p.i.; pink: therapy starting point at day 6 p.i.;

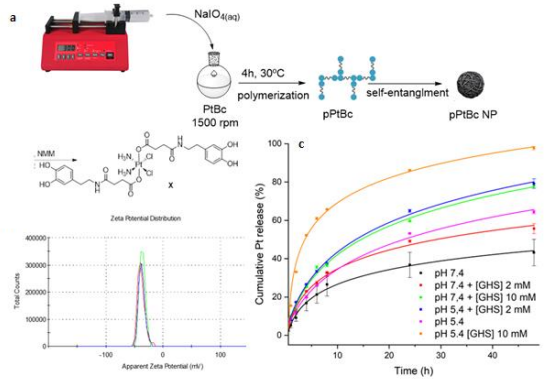

Figure 3. (a) Scheme of the Pt-Fe NCPs synthesis upon polymerization of a Pt(IV) prodrug with sodium periodate. (b) zeta potential of the pPtBc NCPs nanoparticles. (c) Cumulative release profiles of Pt from pPtBc NCPs at 37 ◦C a using the dialisys method in the absence or presence of glutathione (GHS) and at pH 7.4 and pH 5.4