Development of Platinum(IV) conjugates of oxaliplatin and Superoxide dismutase (SOD) mimics as anticancer agents with reduced neurotoxicity

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Platinum-based anticancer agents, such as oxaliplatin (Ox), are widely used in clinic (with a main indication in metastatic colorectal cancer for Ox), despite severe side effects and the emergence of resistance. The major dose-limiting adverse side effect of Ox is the Ox-induced peripheral neuropathy (OIPN).[1] Its underlying molecular mechanisms are complex and no clinically effective treatment or prevention therapy exists.[2] Ox and other Pt based anticancer drugs have been shown to produce a burst of intracellular oxidative stress leading to cancer cells' death because of their higher sensitivity to the increased oxidative stress.

Several modulators of the redox balance have demonstrated interesting results in counteracting Ox-induced neurotoxicity.[3] Manganese Superoxyde Dismutase (SOD)-mimics are low molecular weight Mn complexes able to reproduce *in vivo* the activity of the MnSOD, a metalloenzyme involved in the cellular protection against oxidative stress, in catalyzing the dismutation of the anion superoxide into H_2O_2 and O_2.[4]

We explore the relevance of SOD mimics to reduce Ox side effects and increase its therapeutic index. We have recently described that the combined treatment of Ox

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with the MnSOD mimic Mn1 developed in our group,[5] prevented the appearance of sensitive axonal neuropathy and neuromuscular disorders induced by Ox, in mice.[6] We now develop covalent conjugates between MnSOD mimics and Ox in the shape of Pt(IV) prodrugs[7,8] for a better control and targeting of both active components inside cells and tumors. Our last results and progress in that direction will be presented.