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CIC biomaGUNE
CENTER FOR COOPERATIVE RESEARCH IN BIOMATERIALS

seminar

Monday, 5th November, 12.00 pm, Seminar Room

Host: Prof. Luis M. Liz-Marzán

Bioorthogonal photocatalytic activation of metal-based anticancer agents

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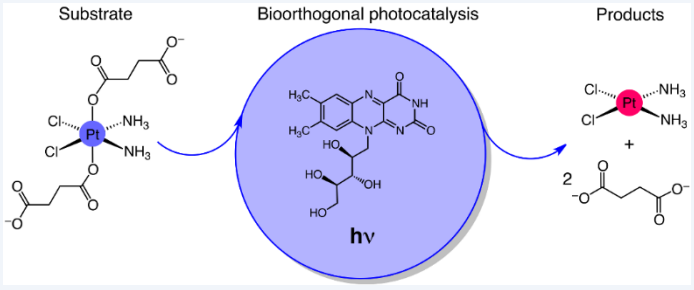
Photoactivatable Pt^{IV} antitumour agents are widely studied as prodrug candidates and have a relevant role in preclinical practice. They undergo photoreduction into cytotoxic Pt^{II} species (e.g. cisplatin) when irradiated with UV light, potentially reducing side-effects of systemic chemotherapies. Nevertheless, two intimately related photochemical features for this class of compounds need to be improved for advancing their use towards application. On the one hand, tissue penetration needs to be enhanced by red-shifting excitation wavelengths, while on the other, photochemical efficiency has to be optimized to reduce irradiation time.

Herein in this PhD work, we report a new approach based on bioorthogonal photocatalysis to overcome such photophysical limitations in Pt^{IV} anticancer complexes. We have discovered that co-administration of the exogenous biological photosensitizer riboflavin (Rf) with Pt^{IV} prodrugs under 460-nm light irradiation achieves efficient photocatalytic conversion of Pt^{IV} into cytotoxic Pt^{II} species in biological environments. Results shows that the biorthogonal couple Rf/Pt^{IV} induces anticancer activity comparable to cisplatin with a light dose as low as 0.36 J·cm^{-2}, 15-35 times lower than those typically used for UVA and blue light activation. Importantly, this bioorthogonal photoreaction does not decrease its efficiency when performed in cell culture media. After these findings, insights into their biological activity *in vitro* and mechanism were studied. Results showed that the photocatalysis induced an antiproliferative effect in Capan-1 cells comparable to cisplatin but suggesting additional alternative cell death pathways.

As flavins in cells are incorporated into the flavin binding pocket of the flavoproteins as cofactors, we explored the capability of different flavoproteins (miniSOG, NOX, GOX and Glutathione Reductase) to act as photocatalysts of these Pt^{IV} substrates. The different behaviour of the flavoproteins was explained by their accessibility to the binding pocket and the calculated surface charge areas of the surrounding of the binding pockets. Remarkably, NOX is able to catalyse Pt^{IV} in the dark when its biological cofactor NADH is used as electron donor. This fact suggests an alternative mode of activation of Pt^{IV} prodrugs inside cells.



Scheme of the photocatalytic approach in w hich the substrate *cis*,*cis*,*trans*-$[Pt(NH_3)_2(Cl)_2(O_2CCH_2CH_2CO_2)_2]^{2-}$ is photoactivatedwith 460-nm light in the presence of the photocatalyst Rf.