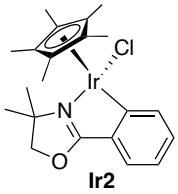
Conception and application of innovative strategies for selective targeting and delivery of iridium-based compounds with anticancer properties

Context

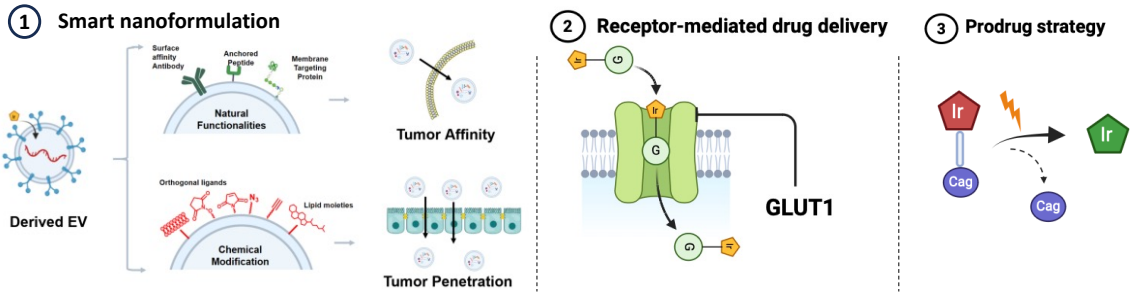
Following the introduction of the chemotherapeutic agent cisplatin in the early seventies, a wide range of metal-based compounds have been found to display cytotoxic properties on cancer cell models and even on animal models. However, very few of them underwent clinical trials, one of the main reasons being their poor selectivity to cancer cells with respect to "healthy" cells. In the ChemBio team at Sorbonne Université, we introduced a new series of "half-sandwich" iridium(III)-based compounds with promising antiproliferative activity on 2D and 3D cell cultures.[1] The mechanism of action of the lead compound **Ir2** was determined and the main protein targets were identified using a combination of click chemistry and chemoproteomics.[2] Nevertheless, **Ir2** is nearly as active on cancer cells (HeLa, A2780, A2780cis, Huh-7) and non-tumoral cells (hTERT-RPE1, HEK293), which seriously compromises its future translation to the clinic.



Ir2

Objective

Within the general context of precision medicine, drug development takes more and more into account the particular genomic, metabolic and physiochemical features of cancer cells and the tumor microenvironment. The objective of the proposed PhD project is to elaborate innovative strategies for selective targeting and delivery of cytotoxic iridium-based compounds to cancer cells, so as to improve drug efficacy and prevent possible side effects. To reach this objective, **three approaches** will be deployed: **(1) smart nanoformulation**;[3] **(2) receptor-mediated drug delivery by conjugation of specific ligands**;[4] **(3) prodrug strategy based on the unique metabolism of cancer cells and / or the tumor microenvironment or external stimulus**.



Justification of the scientific approach

In the field of cancer therapy, one of the smartest nanoformulation approaches relies on extracellular vesicles (EVs) to load and deliver cargos, among which chemotherapeutic drugs.[5] EVs are nano-sized vesicles surrounded by a lipid bilayer, secreted by various types of cells and involved in cell-to-cell communications. Most importantly, EVs' composition reflects that of their originating cells, meaning that they display intrinsic targeting abilities. For instance, EVs produced by cancer cells show tropism to their parent cells (=homing capability). Drug loading methods into EVs are now well established as well as EV engineering to further improve their targeting ability, endow their tracking or facilitate their isolation. In the field of metallodrugs, cisplatin encased in microparticles released by apoptotic cancer cells was shown to inhibit ovarian cancer growth in mice.[6] Resistance to cisplatin in lung cancer patients was also reversed by injection of cell-derived microparticles loaded with the drug.[7] EVs produced from A549 lung cancer cells

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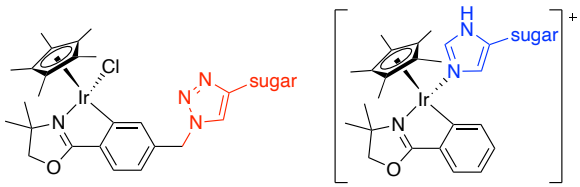
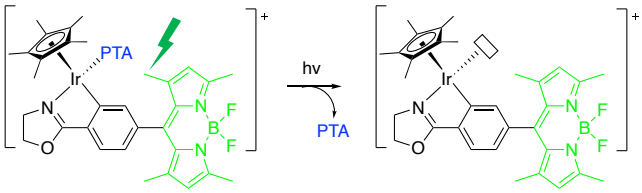
[1] Ramos et al. Dalton Trans. **2020**, 49, 17635
[2] Ramos et al. J. Med. Chem. accepted for publication
[3] Hu et al. Nano Res. **2018**, 11, 5474
[4] R. G. Kenny, C. J. Marmion, Chem. Rev. **2019**, 119, 1058
[5] Walker et al. Theranostics **2019**, 9, 8001
[6] Tang et al. Nature Commun. **2012**, 3, 1282
[7] Ma et al. Cell Res. **2016**, 26, 713

were efficiently loaded with a palladium catalyst cargo. Uncaging of an anticancer prodrug catalysed by the Pd catalyst selectively occurred in A549 cells, resulting in a dramatic decrease of cell viability.[8] In this joint study, the cancer cell- (e.g. A549 etc) based EVs will be developed through the protocols established in NTU partner's team.[9] The surface modification of the developed EVs will be proceeded and their ability to package our lead compound **Ir2** by direct or indirect loading methods will be first investigated. Tracking of EVs loaded with **Ir2** will be aided by metabolic engineering using N-azidoacetyl-D-mannosamine[10] or azide-choline[11] to introduce chemical reporters on the glycoproteins or the phospholipids present at the EV membrane followed by bioorthogonal labelling with a suitable fluorophore.

Cancer cells are characterized by their dependence to anaerobic glycolysis for their survival and growth (Warburg effect), which requires intake of high amounts of glucose and in turn overexpression of glucose transporters. Hence, glycoconjugation has been found to increase both the activity and selectivity of platinum- and ruthenium-based drugs.[4] It was shown that the C-2 position of D-glucose was the optimal place for conjugation of the anticancer drug oxaliplatin for effective uptake and selective activity towards cancer cells.[12] We will take advantage of the previously developed "clickable" derivative of **Ir2** to synthesize D-glucose bioconjugates with different linkers. Alternatively, the sugar entity will be introduced via an imidazole ligand. Antiproliferative activity and cell uptake will be investigated and systematically compared to **Ir2**.



The cytotoxic activity of **Ir2** and its congeners is directly related to the presence of a labile position (occupied by the Cl ligand in **Ir2**) responsible for both its catalytic activity and ability to bind to target proteins.[2] A possible prodrug strategy is to design a complex for which occupation of the labile position may be controlled at will via an internal or an external stimulus. For instance, we will design photoactivatable iridium complexes that may undergo monodentate ligand decoordination upon light irradiation. An example of such a complex comprises a BODIPY-containing chelating ligand providing the light-harvesting antenna and a water-soluble phosphine ligand (PTA). By analogy with the literature on related half-sandwich complexes,[13] we anticipate that light irradiation at the absorption wavelength of BODIPY may trigger the release of the PTA ligand (i.e. photo-uncaging) and in turn stimulate the complex cytotoxicity.



Interest in the collaboration between NTU and Sorbonne Université

This PhD project relies on the complementary competences and skills of the groups of M. Salmain (Chembio team, IPCM, Sorbonne Université) and B. Xing (School of Chemistry, Chemical engineering and Biotechnology (CCEB, Nanyang Technological University) in molecular chemistry, medicinal chemistry and chemical biology, more precisely in the development of innovative therapeutic strategies for precision medicine. Both teams will contribute equally to the PhD project, with chemistry done in Paris and advanced cell biology and engineering done in Singapore.

Candidate profile

Applicants must hold a Master degree (or equivalent) in chemistry with a strong interest in medicinal chemistry. Additional competences in chemical biology or cellular biology will be an asset. Candidate selected will be trained for interdisciplinary studies in the field of medicinal chemistry, drug delivery and nano-medicine.

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[8] Sancho-Albero et al. Nature Catal. **2019**, 2, 864
[9] Lyu et al. Bioconjugate Chem. **2018**, 29, 2715; and 2022-045-01-SG PRV
[10] Song et al. Bioconjugate Chem. **2020**, 31, 1562; Ai et al. Angew. Chem. Intl. Ed. **2017**, 56, 3031
[11] Zhang et al. Anal. Chem. **2018**, 90, 11273
[12] Patra et al. J. Am. Chem. Soc. **2016**, 138, 12541
[13] Deo et al. Organometallics **2016**, 35, 2694