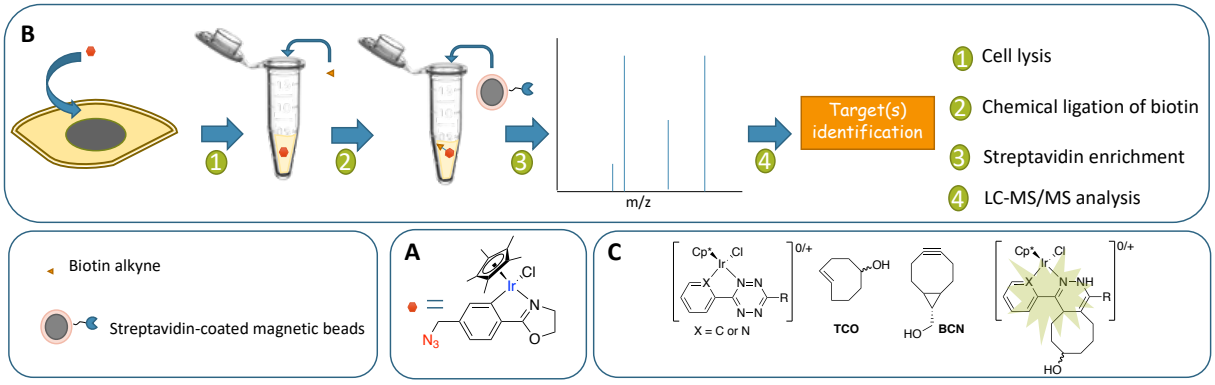
One-year post-doctoral position available in the ChemBio team of the Institut Parisien de Chimie Moléculaire, Sorbonne Université, Paris, France

Project title: Half-sandwich iridium(III) complexes as anticancer drug candidates: intracellular tracking and identification of protein targets by chemical proteomics

Context: Iridium(III) complexes are increasingly regarded as valuable alternatives to platinum-based anticancer drugs owing to their presumably different mode of action. Various so-called "half-sandwich" complexes display moderate to high antiproliferative activity on cancer cell cultures, mostly depending on their coordination sphere and less on their charge. A pharmaco-genomic study carried out with iridium complexes carrying a C^N or a N^N chelating ligand revealed that they act by induction of ROS production that translates into upregulation of antioxidant response and DNA damage.

Project: We recently introduced a library of neutral half-sandwich iridium complexes comprising diversely substituted phenyloxazoline (phox) ligands. They show a similar antiproliferative activity on HeLa cervix cancer cell cultures with IC_{50} ranging from 3 to 6 µM. However, only some of the complexes elicit rapid and long-lasting intracellular production of H_2O_2, presumably via a catalytic mechanism. This indicates that oxidative stress is partly responsible for the cytotoxicity of this family of complexes. In addition, the presence of an available coordination site makes these complexes reactive towards biological nucleophiles, such as proteins. Thus, the ability to covalently bind to selected proteins could also be responsible for the complexes' cytotoxicity. The first part of the project will consist in setting a chemical proteomics approach with an iridium complex carrying a bioorthogonal azide handle **A** on its chelating ligand to identify protein targets (workflow schematized in **B**). We also demonstrated by high resolution fluorescence microscopy that a BODIPY-tagged iridium complex selectively accumulated in membranous organelles inducing ER stress response and finally cell death by apoptosis. However the lipophilic nature of the BODIPY entity may have severely biased the distribution of the complex in cells. A less invasive strategy would consist in labeling the complex once inside the cells. The inverse electron demand Diels-Alder reaction between tetrazines and strained alkenes/alkynes is well suited to this purpose as it is compatible with in vivo conditions and may generate fluorescent adducts from non-fluorescent reagents. The second part of the project will deal with the synthesis of 2-phenyl and 2-pyridyltetrazine iridium complexes **C**. Their reactivity with strained alkenes (such as transcyclooctene, TCO) and alkynes (such as bicyclononyne, BCN) will be investigated as well as their effect on cancer cell proliferation. Eventually in-cell bioorthogonal reactions with TCO- and BCN-containing derivatives will be monitored by fluorescence microscopy.



Profile: Applicants should hold a PhD in chemistry and less than 3 years' postdoctoral experience. They should demonstrate a strong expertise in organic / organometallic chemistry. Additional competences in chemical biology will be an asset. Salary: 2590 – 2970 euros / month excluding taxes. Candidates should send their detailed (2-page) CV, a letter of motivation and two letters of recommendation by email to Dr Michèle Salmain (michele.salmain@sorbonne-universite.fr). Deadline for application: November 15, 2021; interviews between Nov 16 and Nov 30, 2021; provisional contract start: February 1st, 2022.