Sorbonne Université/ China Scholarship Council program 2020

Thesis proposal

Title of the research project: Metal carbonyl complexes – nanoparticles conjugates as CO-releasing theranostics (THERACORM)

Keywords: organic and organometallic syntheses, nanoparticles, spectroscopy, biological studies in cells, CO-release

Joint supervision: no

Joint PhD (cotutelle): no

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Doctoral school (N°+name): ED 406 Chimie moléculaire Paris Centre

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SORBONNE UNIVERSITÉ

Subject description (2 pages max):

1) Study context

Metal carbonyl M(CO)s complexes, on their own or upon conjugation onto nanoparticles (NP), have been mainly developed in a biological context as radiopharmaceuticals, biolabels and bio-imaging probes using various modalities such as luminescence, mid-IR, SERS (Surface-enhanced Raman spectroscopy) and photoacoustics.[1] These sensing modalities make use of various characteristics of these complexes: MLCT transitions (when ligands with low lying π^* orbitals are introduced) for luminescence, their strong CO stretches in the mid-IR for Mid-IR and SERS imaging and M-M $\sigma \rightarrow \sigma^*$ transitions of M(CO) clusters in the NIR in the case of photoacoustics. They are also being explored as the most promising candidates as CO-releasing molecules (CORMs).[2] CORMs are molecules able to release CO in a controlled way under certain conditions. The therapeutic beneficial effects of a controlled delivery of low amounts of CO (eg anti-inflammatory and vasodilatation) are well established in conditions such as cardiovascular diseases, inflammatory disorders, organ transplantations... CORMs can release CO in response to various triggers: temperature, ligand exchange, pH change, enzymatic activity and light irradiation. In this latter case, they are called photoCORMs.[3] Critical issues in the development of CORMs for therapeutic applications are their cytotoxicity, stability in solution, delivery to specific targets, a suitable half-life of CO release, the nature and effects of the CORM degradation products after the CO release and the wavelength of light irradiation in the case of photoCORMs, some of these still being key challenges.

2) Details of the proposal

In this collaborative project with Prof. Weng Kee Leong at NTU Singapore, we propose an original approach towards the development of Au nanoparticles conjugated to photoCORMs as theranostics: the platform will combine tunable CO-release properties and stabilized photoproducts, it will enable the study of their cell uptake, localization and CO-release activity in a biological context using luminescence or SERS, while being non-toxic and decorated for specific delivery. Such an integrated approach has not been explored in this field and will contribute to the development of new delivery agents with both imaging and therapeutic abilities, and will provide a better understanding of CORMs interactions with biological environments.

<u>1. Design and characterization of the photoCORMs:</u>

The CO-releasing agents will be photoCORMs based on different M(CO)s systems developed by the partners suitable for SERS detection or CO-release detection by luminescence for example. Wavelength of irradiation and half-life of CO release are critical parameters to optimize. Examples of complexes that will be studied are derivatives of rhenium and manganese tricarbonyl $[Mn(CO)_3(X)(L)]$ complexes developed in the Laboratoire des Biomolécules as multimodal probes for imaging[4,5] and CO_2 electroreduction catalysts[6]. Different X ligands and heteroaromatic L ligands will be explored. The CO release from these complexes will either turn off the luminescence of the degrading complex or turn on the fluorescence of the decoordinated ligand. Ru / Os complexes and M(CO)s nanoclusters, well suited for SERS or photoacoustic detection will also be evaluated.[7] The CO-releasing properties of the complexes – spontaneous and under various photo-irradiations will be monitored as classically performed, using time-dependent IR and UV-Vis spectroscopy along with the UV-Vis myoglobin assay. DFT and TD-DFT calculations will be performed to help in the rational design of complexes with suitable properties.

<u>2. Conjugation with NP and characterization:</u>

The conjugation of a CORM to a carrier may enhance its stability and half-life.[8] The conjugation may also stabilize the photoproducts generated after CO release by acting as a pseudo-ligand, and this can in turn

reduce the detrimental side effects. Specific delivery to a biological target can be achieved through suitable functionalization of the NP (with peptides or proteins). Moreover, increased penetration could be achieved based on the 'enhanced permeability and retention (EPR) effect'. The use of Au NP as a platform is appealing as their optical properties can be tuned by varying their shape, size or environment, their synthesis is well documented and they are highly stable with a low toxicity.[9] The emission quenching ability of the Au NP can be modified with their diameter such that emissive conjugates can be prepared.[10] M(CO)s complexes with interesting photoCORMs properties will be conjugated with Au NP, via a direct reaction (Au-M bond) or via Au-S bond for example (diimine or axial ligand functionalized by a thioester or thioctic acid terminated side chain). The prepared conjugates will be characterized by diverse techniques such as Fourier transform infrared spectroscopy, UV-Vis and fluorescence spectroscopies, dynamic light scattering, transmission electron microscopy or energy-dispersive X-ray analysis.

3. Biological studies and Imaging:

The cytotoxicity of the complexes and conjugates will be evaluated in different cell lines (HT29, A549 etc). Oxidative stress levels (ROS, Nrf2 level and transcriptional activity) and anti-inflammatory response (inflammation markers) will be evaluated. Luminescence imaging in cells will be performed, IR imaging[11] and quantification[4] using the specific signatures of $M(CO)_s$ will also be considered.

3) References

1. a) Clède S., Policar C., *Chem. – Eur. J.*, **2015**, *21*, 942; b) Coogan M. P., Zubieta J. *et al*, *J. Labelled Compd. Radiopharm.*, **2014**, *57*, 255; c) Patra M., Gasser G., *ChemBioChem*, **2012**, *13*, 1232; d) Hostachy S., Delsuc N. *et al*, *Coord. Chem. Rev.*, **2017**, *351*, 172; e) Lam Z., Leong W. K. *et al*, *Analyst*, **2016**, *141*, 1569; 2. Ling K., Ye D.-W *et al*, *J. Med. Chem.*, **2018**, *61* (7), 2611; 3. a) Wright M.A., Wright J.A., *Dalton Trans.*, **2016**, *45*, 6801; b) Marhenke J., Works C. *et al*, *Coord. Chem. Rev.*, **2016**, *306*, 533; 4. a) S. Clède, C. Policar *et al*, *Chem. Eur. J.* **2014**, *20*, 8714; b) S. Clède, C. Policar *et al, Chem. Commun*, **2015**, 2687; c) L. Henry, C. Policar *et al*, *Bioconjugate Chem.,* **2018**, *29* (4), 987; 5. a) Bertrand H. C., Policar C. *et al*, *Inorg. Chem.*, **2014**, *53* (12), 6204; b) He M., Bertrand H.C. *et al*, *New J. Chem.*, **2018**, *42*, 11312; 6. Ching H. Y. V., Fontecave M. *et al*, *Inorg. Chem.* **2017**, *56* (5), 2966; 7. Kong K. V., Leong W. K., Olivo M. *et al*, *Angew. Chem. Int. Ed.*, **2012**, *51*, 9796; 8. Kautz A.C., Kunz P.C., Janiak C., *Dalton Trans.*, **2016**, *45*, 18045; 9. Dreaden E. C., El-Sayed M. A. *et al*, *Chem. Soc. Rev.*, **2012**, *41*, 2740; 10. Hallett A. J., Pope S. J. A. *et al*, *Chem. Commun.*, **2009**, 4278; 11. a) Kong K. V., Leong W. K. *et al*, *Bioconjugate Chem.*, **2007**, *18* (5), 1370; b) Marcelli A., Petibois C. *et al*, *Biotechnol. Adv.*, **2012**, *30* (6), 1390

4°) Profile of the Applicant (skills/diploma…)

We are looking for a candidate with a master degree in chemistry interested in multidisciplinary projects involving synthesis, spectroscopy, nanoparticles conjugation and characterizations and biological studies. Skills in organic synthesis and knowledge in UV-Vis, fluorescence spectroscopies are required along with a willingness to work in different environments involving short stays at NTU Singapore. A good level in English, strong motivation, adaptability and interpersonal communication skills are essential.

Contacts:

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