Application to be sent to Claire Mendoza and Clemence Grosnit:
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Deadline: March 1st, 2024

EUR CARe PhD program pre-proposal

(2 pages maximum)

PhD Director: Florence BEDOS (Pr, UT3), florence.bedos@univ-tlse3.fr
(Name and email)

PhD Director affiliation: SPCMIB, UMR CNRS 5068, Université Paul Sabatier (https://spcmib.univ-tlse3.fr/equipe-magenta-3)

PhD co-Director: May Lee LOW (Associate-Professor), lowml@ucsiuniversity.edu.my
(Name and email)

PhD co-Director affiliation: Faculty of Pharmaceutical Sciences, UCSI University Kuala Lumpur, 56000 Cheras, Kuala Lumpur, Malaysia (https://www.ucsiuniversity.edu.my/assistant-professor-dr-low-may-lee)

Research project title: *Rhenium complexes as efficient candidates against pancreatic cancer*

Research program abstract (494/500 words):

Since the discovery of cisplatin in the 60s and its use as an anti-cancer agent, a great deal of research has been focused on the development of new metal-based anti-cancer drugs. Numerous metal complexes (based on platinum, ruthenium, gold, iridium and more recently rhenium) have been developed and tested biologically. Besides, the efficacy of metal-based drugs in the treatment of cancer should not be underestimated, as they have recently been used in around 32 of the 78 anti-cancer regimens (R. Kanaoujiya *et al.*, *Mater. Today: Proc.* **2023**, *72*, 2822−2827).

Among the metal complexes studied, rhenium complexes, particularly those based on tricarbonyl(I)rhenium cores, are particularly promising and seem to be a viable alternative to platinum-based anticancer drugs for application in medicinal chemistry as they have shown cytotoxic and phototoxic properties against malignant cells (P. Collery *et al.*, *Curr. Pharm. Des.* **2019**, *25*, 3306−3322). Moreover, the tricarbonylrhenium(I) complexes are thermodynamically stable and kinetically inert (*i.e.* they are not really affected by the reactive species present in their chemical environment), and exhibit particular (photo)physical properties make them very attractive as imaging probes (luminescence) and/or as therapeutic drugs (for PDT or in radiotherapy with radioactive complexes based on the ^{188}Re isotope) (A. Sharma *et al*., *RSC Adv.* **2022**, *12*, 20264).

Our team has recently developed a new family of rhenium(I) complexes based on a pyridinetriazole bidentate chelator (called pyta) with the general formula [Re(CO)$_3$(pyta)X] (X = halogen or phosphine group). They are highly emissive and show rare aggregation-induced phosphorescence enhancement (AIPE) behaviour when X = Cl (J. Wang *et al.*, *Dalton Trans.*, **2019**, *48*, 15906-15916) or can be used as CO-releasing photoactive molecules (photoCORMs) when X is a phosphine group (A. Hernandez-Meijas *et al.*, *Dalton Trans.*, **2021**, *50*, 1313-1323). In the latter case, the release of the toxic CO group is accompanied by the production of singlet oxygen. More interestingly, an initial screening of the anti-cancer properties of these rhenium complexes was carried out by our Malaysian partner, and showed promising cytotoxic properties against several cancer cell lines such as HT29 (colon), A549 (lung) and SW190 (pancreas), with interesting selectivity indexes for some of them (*manuscript in preparation).* As example, a tricarbonylrhenium(I) complex based on a pyta derivative bearing a pendant phenylbenzoxazole unit exhibited a promising selectivity index of 4.16 for SW190 cell line.

Based on these promising initial results, further studies should now be pursued with the development of a second generation of rhenium(I) complexes in order to (i) optimize the SI, (ii) establish a structure-activity relationship between the chemical structure of the complexes and their anti-cancer properties, and (iii) determine the mechanism of action, in particular against the pancreatic cell line. To this end, computational chemistry (collaboration with Dr. M. Wolff, University of Vienna) will be integrated into our approach in order to define the most relevant chemical modifications (of the chelating ligand or the ancillary ligand X) prior to any synthesis of Re(I) complexes by our group and their biological evaluation by the Malaysian partner.

Describe in 50 words max for each how this project fits the 3 defining criteria of the CARe graduate programme:

1) Relation to CARe topics of Cancer, Ageing and/or Rejuvenation

This project focuses on the development of efficient anti-cancer probes using a disruptive and pluridisciplinary approach combining DFT and experimental chemistry as well as biological and mechanistic studies.

2) Multidisciplinary aspect

This project will be carried out by two complementary units, one in Chemistry (France) and the other in cancer activities evaluation (Malaysia). The French team will synthesise new tricarbonylrhenium compounds, while the Malaysian team will be in charge of their anticancer activity evaluation and their action mechanism determination.

3) International and/or industrial aspect(s)

The project will be developed either as an international PhD co-supervision, or as a "co-tutelle" agreement between both Paul Sabatier and UCSI (Malaysia) Universities. The PhD student will spend 9 to 12 months at UCSI University. An MoU between both institutions is currently being signed at UT3.

5 keywords in line with EUR CARe

Cancer, therapy, international network, pluridisciplinarity, bioinorganic chemistry

5 references of the teams, highlighting the co-signatory students:

(Last 5 years) 3 papers from French team + 2 from Malaysian team (co-author Master2 or PhD students highlighted in green)

1. Reduced Schiff-base derivatives to stop the reactive oxygen species production by the Cu(Aβ) species: a structure activity relationship; M. Lefèvre, L. Lantigner, L. Andolfo, C. Vanucci-Bacqué, C. Esmieu, Eric Benoist F. Bedos-Belval, C. Hureau; *C.R. Chimie*, **2023**, 1-11. https://doi.org/10.5802/crchim.255

2. Luminescent *fac*-[Re^{I} X(CO)$_3$(phenyl-pyta)] (X = Cl, Br, I) complexes: Influence of the halide ligand on the electronic properties in solution and in the solid state, A. Poirot, C. Vanucci-Bacqué, B. Delavaux-Nicot, N. Saffon-Merceron, C.-L. Serpentini, N. Leygue, F. Bedos-Belval, E. Benoist, S. Fery-Forgues, *Photochem. Photobiol. Sci.*, **2023**, *22*, 169-184; https://doi.org/10.1007/s43630-022-00307-y

3. Phenyl-1,2,4-pyta-tricarbonylrhenium(I) complexes: Modifications of a convenient basic unit for tuning the photoluminescence and waveguiding properties, A. Poirot, C. Vanucci-Bacqué, B. Delavaux-Nicot, N. Leygue, N. Saffon-Merceron, F. Alary, F. Bedos-Belval, E. Benoist, S. Fery-Forgues, *Dalton Trans.*, **2021**, *50*, 13686-13698; https://doi.org/10.1039/D1DT02161C

4. Novel gemcitabine-Re(I) bisquinolinyl complex combinations and formulations with liquid crystalline nanoparticles for pancreatic cancer photodynamic therapy, Liew, H.S., Mai, C.W., Zulkefeli, M., Madheswaran, T., Kiew, L.V., Pua, L.J.W., Hii, L.W., Lim, W.M. and Low, M.L., *Front. Pharmacol.* **2022**, *13*, 1-14; https://doi.org/10.3389/fphar.2022.903210

5. Recent emergence of rhenium(I) tricarbonyl complexes as photosensitisers for cancer therapy, Liew, H. S., Mai, C. W., Zulkefeli, M., Madheswaran, T., Kiew, L. V., Delsuc, N., and Low, M. L. *Molecules* **2020**, *25*, 4176; https://doi.org/10.3390/molecules25184176