PhD proposal 2019 – Ecole Doctorale de Chimie – Université Claude Bernard Lyon 1

Développement d'outils théranostiques activables par rayonnements ionisants pour le traitement du cancer

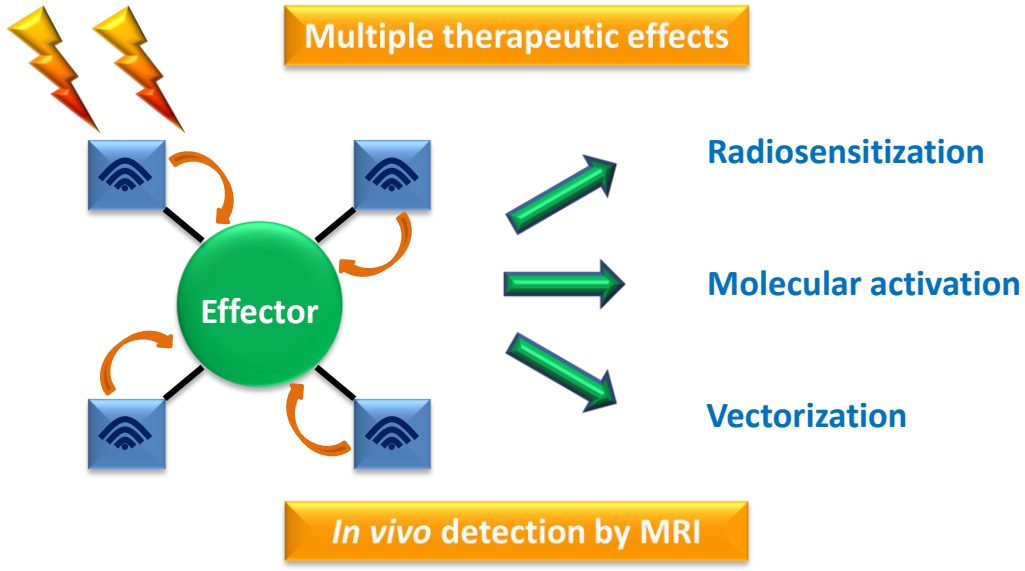
Development of ionizing radiation-triggered theranostic tools for cancer treatment

Supervisor : Dr Ulrich Darbost (ulrich.darbost@univ-lyon1.fr)

Co-supervisor : Dr Guillaume Bort (guillaume.bort@univ-lyon1.fr)

The possibility to control *in vivo* activation of a treatment in space and time with limited secondary effects could have a major impact in cancer medicine. This could be achieved if specific molecular activations or release of specific drugs could be induced by external stimuli. These challenges have already been successfully addressed in the research field of photochemistry.[1-2] Indeed, hundreds of light-sensitive systems have been described in the literature such as caged-compounds, photoswitches and molecular machines. Nevertheless, all the systems described in the literature up to date can only be efficiently activated by ultraviolet, visible or near-infrared lights. These light energies limit *in vivo* activation to few hundred micrometers below the skin and, except for epidermal and ocular treatments, no clinical applications of these light-sensitive systems can be proposed without using invasive probes to deliver light inside the tissues.

The PhD project aims at developing a **theranostic tool able to provide treatment in deep tissues in a perfectly space- and time-controlled way**. Theranostic nanoparticles (NPs) or molecules detectable by nuclear magnetic resonance imaging (MRI) and specifically functionalized to trigger orthogonal and combined therapeutic actions upon highly-penetrating external stimuli, will be prepared. The theranostic tools will be activated by **ionizing radiation (IR)** such as **X-rays**, a stimulus which can **penetrate at any depth in the body** and which is currently **available in most of hospitals**. This breakthrough activation method should be able to trigger therapeutic actions such as (i) radiosensitization, (ii) molecular activation and (iii) vectorization.



PhD proposal 2019 – Ecole Doctorale de Chimie – Université Claude Bernard Lyon 1

This project aims at establishing unprecedented ***in vivo*-controlled molecular manipulations** using external stimuli able to penetrate into the biological tissues at any depth. This approach is expected to open new routes for medical practices with real potency for clinical applications and could arise **breakthrough in cancer treatments**, especially for those developing radio/chemical resistances.

This project will give great opportunities for the successful candidate to develop competences in **nanotechnology**, **organic chemistry**, **formulation**, **cell biology** and **photoactivation**. The goal of the PhD project is (i) to gain insight into the mechanisms involved in the original activation process relying on IR-energy conversion and (ii) to develop a theranostic tools detectable by MRI and externally-activated for cancer treatment with the aim to validate an *in vivo* proof of concept during the PhD period.

The candidate will (i) **prepare and characterize** the molecules and NPs at the *Institut Lumière Matière*, (ii) assess their **physical and pharmacological actions upon IRs** and (iii) monitor their **therapeutic actions** on **cancer cells** and **spheroids** at both *Institut Lumière Matière* and *Institut Curie* at Orsay. The *in vivo* studies will be carried out by our collaborators.

The candidate needs to have a strong interest in interdisciplinary sciences at the interface of chemistry and biology. She/he is expected to be highly motivated to take advantages to work in a leading research group in the field of nanotechnology for the development of this ambitious project.[3] Our team is very active in the **development of biomedical pharmaceutics**, as evidenced by the success of the anti-cancer theranostic AGuIX NP, developed by our team and currently used in **two clinical trials of phase I**.[4-5]

The successful candidate will join the group of Prof. Olivier Tillement (FENNEC group, *Institut Lumière Matière*, UMR CNRS 5306) and will be supervised by Dr Ulrich Darbost, Dr Guillaume Bort and Dr François Lux. If you are interested in joining the group, please send your CV and a motivation letter to Dr Ulrich Darbost and Dr Guillaume Bort.

Keywords: theranostic, cancer treatment, nanoparticles, organic chemistry, photoactivation.

References:

1. G. Bort, T. Gallavardin, D. Ogden, P. I. Dalko, *Angew. Chem. Int. Ed.* **2013**, *52*, 4526-4537.
2. G. Bort, S. Mura, P. Couvreur, in *Nanotheranostics for personalized medicine* (Eds.: S. Mura, P. Couvreur), World Scientific Publishing and Imperial College Press, **2016**, pp. 83-114.
3. F. Lux, V. L. Tran, E. Thomas, S. Dufort, F. Rossetti, M. Martini, C. Truillet, T. Doussineau, G. Bort, F. Denat, F. Boschetti, G. Angelovski, A. Detappe, Y. Crémillieux, N. Mignet, B.-T. Doan, B. Larrat, S. Meriaux, E. Barbier, S. Roux, P. Fries, A. Müller, M.-C. Abadjian, C. Anderson, E. Canet-Soulas, P. Bouziotis, M. Barberi-Heyob, C. Frochot, C. Verry, J. Balosso, M. Evans, J. Sidi-Boumedine, M. Janier, K. Butterworth, S. McMahon, K. Prise, M.-T. Aloy, D. Ardail, C. Rodriguez-Lafrasse, E. Porcel, S. Lacombe, R. Berbeco, A. Allouch, J.-L. Perfettini, C. Chargari, E. Deutsch, G. L. Duc, O. Tillement, *Brit. J. Radiol.* **2018**, *91*, 20180365.
4. https://clinicaltrials.gov/ct2/show/NCT02820454.
5. https://clinicaltrials.gov/ct2/show/NCT03308604.