MASTER / Ph. D. THESIS PROPOSAL

***In vivo* detection of reactive oxygen species using multifunctional luminescent nanoparticles**

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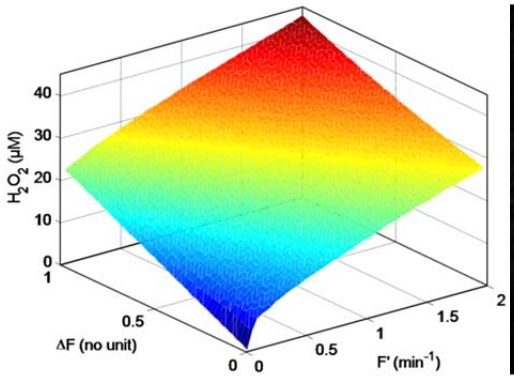
Numerous human pathologies, like inflammatory and neurodegenerative diseases and certain types of cancer, are associated with the production of reactive oxygen species (ROS) and the appearance of oxidative stress. A quantitative ROS detection is therefore crucial for i) the identification of therapeutic targets, ii) the identification of the molecular mechanisms controling the transition to a pathological state, and iii) evaluate the impact of therapeutic approaches. However, obtaining quantitative, space- and time-resolved information on the ROS concentration is difficult because of a lack of efficient ROS detection methods.

We have demonstrated that luminescent Eu-doped nanoparticles detected at the single particle level are efficient ROS sensors allowing quantitative, time- and space-resolved assessment of the intracellular ROS production.[1,2] Our approach is based on Eu-ion oxydoreduction processes leading to a modulation of the nanoparticle emission intensity which can be related to the instantaneous H_2O_2 concentration (see left figure). Moreover, we have shown that $Gd_{0.6}Eu_{0.4}VO_4$ nanoparticles containing both Gd^{3+} and Eu^{3+} ions combine luminescence and ROS sensing properties with the ability to significantly increase contrast in MRI images (see right figure).[3]



The aim of this M2/PhD thesis is to transpose ROS detection to the *in vivo* level, in particular in the case of malignant tumors, as a tool for the analysis of the evolution of these pathologies. This will also involve exploring new nanoparticles and synthesis strategies, novel detection schemes at the level of an ensemble of nanoparticles and the optimization of their optical and sensing properties. We will inject nanoparticles in tumors and in neighboring tissues in mice to evaluate the ROS production as a function of localization (center or periphery of the tumor), of the tumor development stage and of anti-tumoral treatments to establish a diagnostic indicator of disease severity and its evolution.

This interdisciplinary project is based on a network of collaborations with the Laboratory of Condensed Matter Physics (T. Gacoin, synthesis and nanoparticle characterization), the Gustave Roussy Cancer Campus (C. Laplace-Builhé, cancer mouse models) and with the Paris Cardiovascular Research Center (P.-L. Tharaux, O. Clément, inflammation mouse models, MRI imaging). The M2/PhD student will have the opportunity to acquire and exploit a broad range of competencies in nanomaterial development and in biological imaging.

1. D. Casanova, C. Bouzigues, T.-L. Nguyên, R. O. Ramodiharilafy, L. Bouzhir-Sima, T. Gacoin, J.-P. Boilot, P.-L. Tharaux, A. Alexandrou, *Single europium-doped nanoparticles measure temporal pattern of reactive oxygen species production inside cells,* Nat. Nanotech. 4, 581-585 (2009)
2. C. I. Bouzigues, T.-L. Nguyên, R. Ramodiharilafy, A. Claeson, P.-L. Tharaux, A. Alexandrou, *Regulation of the ROS Response Dynamics and Organization to PDGF Motile Stimuli Revealed by Single Nanoparticle Imaging,* Chem. Biol. **21**, 647-656 (2014)
3. M. Abdesselem, M. Schoeffel, I. Maurin, R. Ramodiharilafy, G. Autret, O. Clément, P.-L. Tharaux, J.-P. Boilot, T. Gacoin, C. Bouzigues, A. Alexandrou, *Multifunctional rare-earth vanadate nanoparticles: luminescent labels, oxidant sensors, and MRI contrast agents,* ACS Nano (2014)