ECOLE DOCTORALE "Médicament, Toxicologie, Chimie, Imageries"
- UNIVERSITE PARIS DESCARTES
Proposition de sujet de thèse à l'appui d'une demande de contrat doctoral 2018-2019

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Titre du sujet de thèse proposé : Development and applications of EPR probes of oxidative stress.

Contenu scientifique du programme de la thèse

The level of reactive oxygen species, such as superoxide anion and hydroxyl radical, is tightly regulated by antioxidant enzymes or small molecules *in vivo*. However, when the balance is lost, a situation of oxidative stress can occur in cells with accumulation of damages to proteins, lipids, and nucleic acids. These lesions can be analysed by *ex vivo* methods and oxidative stress is involved in a large number of pathological situations (inflammation, cancer, neurodegenerative diseases...). The non-invasive detection and mapping of oxidative stress *in vivo* would give valuable information on disease development and help develop diagnostic and therapeutic tools.
In recent years, we focused on developing new redox-sensitive probes derived from tetraethyl-substituted aminoxyl radicals (nitroxides) or hydroxylamines to monitor oxidative stress by differential measurements on pathological and control animals by electron paramagnetic resonance (EPR) spectroscopy. The previous PhD project allowed us to perform a structure-activity relationship study and to validate the hypothesis with the lead compound on cultured cells. This opens the way for the current PhD project focused on further probe optimization and *in vivo* applications.

Task 1: Redox-sensitive EPR probe synthesis

The first objectives of the PhD project will be:

- to synthesize new probe structures with increased bioavailability (e.g. including esterase-sensitive groups that enable higher intracellular accumulation);
- to scale up the synthesis of the best probe candidates for EPR in rodents;
- to synthesize ^{15}N- and/or ^{2}H-analogues of the best probes to increase the sensitivity of *in vivo* EPR.

Task 2: In vitro evaluation of the probes

We will further characterize the probe mechanism of action *in vitro* (with model systems of oxidative and reduction cellular processes), in cultured cells and tissues.

Task 3: In vivo application to animal models

In collaboration with C. Roques (UMR CNRS 8258 / Inserm U1022, Paris Descartes), we will develop an appropriate formulation strategy for intravenous injection of the lipophilic probes (e.g. nano-emulsions).

We will assess the *in vivo* biostability and distribution of the probes on control animals before developing the application to rodent models of oxidative stress (with first *ex vivo* then *in vivo* EPR detection). A special focus will be set on cardiovascular diseases thanks to the collaboration with I. Rémy-Jouet (Inserm U 1096, Université de Rouen-Normandie).

Informations sur le concours de l'école doctorale

http://ecolesdoctorales.parisdescartes.fr/ed436/Postulants-a-l-ED/Contrat-doctoral/Informations-pratiques

La date limite pour le dépôt de candidature : 14 mai 2018- 17h (prendre contact avec F. Peyrot au préalable).