

Thesis Proposal (2018-2021) at Institute of Analytical Sciences – Lyon – France
Ecole doctorale de Chimie de Lyon (ED206)

Title: Numerical and experimental approaches for the study of human peroxiredoxins inhibition by natural and synthetic catechols

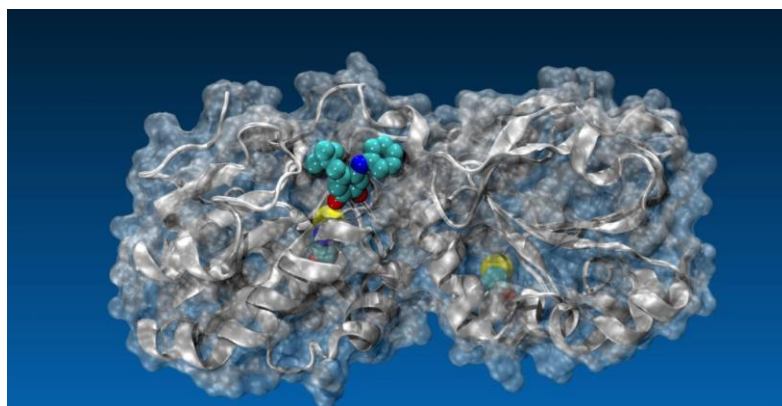
(Approches numériques et expérimentales pour l'étude de l'inhibition des peroxyrédoxines humaines par des catéchols naturels et synthétiques.)

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Catechols belong to the family of natural polyphenols believed to be antioxidant protecting the organism from oxidative stress. We evidenced that simple catechols are able to bind to the active site and to inhibit human peroxyredoxins (hPrx)^{1,2}. These enzymes are involved in the control mechanisms of the intracellular redox homeostasis and are showed to be potential therapeutic targets in some cancers and more recently in cerebral post-ischemic inflammation^{3,4}.

A lot of natural and synthetic products with catechol subunits are available in different databases (*chimiothèque nationale du CNRS*, Chemical Abstracts and others). We propose to screen these databases with a new numerical strategy using molecular dynamics⁵. The best molecules will be then sourced and their affinity for the hPrx and their effect on inhibition will be studied using solution NMR and enzymatic assays². The interaction specificity for the six different hPrx, presenting different oligomerisation states in the cell⁶, will be also studied.



Structure of hPrx5 complexed to a synthetic catechol occupying its active site

The PhD will be developed in the research group Interact at ISA, Lyon-Villeurbanne, France within a network of international collaborations including an innovative company specialized in drug discovery.

The suitable candidates will have a Master degree optimally in chemistry or biochemistry, physical-chemistry, computational chemistry or biochemistry with a particular interest and motivation for analysis using calculations and experimental approaches (NMR, kinetics assays,...).

References:

1. Troussicot, L. ; Guillière, F. ; Limongelli, V. ; Walker, O. ; Lancelin, J-M. *JACS*, 2015, 137, 1273
2. Chow, M.L. ; Troussicot, L. ; Martin, M. ; Doumèche, B. ; Guillière, F. ; Lancelin, J-M. *Biochemistry*, 2016, 55, 3469-3480
3. Garcia-Bonilla, L. ; Ladecola, C. *Nat Med*, 2012, 18, 858-9
4. Knoops, B. ; Argyropoulou, V., Becker S., Ferte L., Kuznetsova O. *Mol. Cells*, 2016, 39, 60-4
5. De Vivo M., Masetti M., Bottegoni G., Cavalli A. *J. Med. Chem*, 2016, 59, 4035-4061



6. Tairum, C. A.; Santos, M.C.; Breyer, C.A.; Geyer, R.R.; Nieves, C.L.; Portillo-Ledesma, S.; Ferrer-Sueta, G.; Toledo, J. C. Jr.; Toyama, M. H.; Augusto, O.; Netto, L.E.; De Oliveira, M. A. *Nature Scientific reports*, 2016, **6**, 33133.