POSTDOCTORAL FELLOWSHIP

OPEN POSITION

DESCRIPTION

Project *Iron-PepOx*: Iron(III)-chelating model peptides as bioinspired antioxidants.

CONTEXT: Metal ions are naturally occurring in living organisms and play pivotal roles in a plenty of physiological processes, including photosynthesis, respiration, metabolism, transmission of nervous influx or even protection against pathogenic agents. Functions endorsed by the metal ions depend on their physicochemical properties such as their charge, size or electronic properties. Among the transition metal ions having an *in vivo* role, iron and copper are associated with several biological processes. Indeed, while copper is present at a trace level in the human body, it is involved as cofactor in redox enzymes (*e.g.*, galactose oxidase, superoxide dismutase) and in neurotransmission. Concomitantly, iron is essential for the respiratory chain as a key component of both hemoglobin and myoglobin.

Since metal ions play central roles in living organisms, the misregulations of their concentration, homeostasis or metabolism can trigger several pathologies. As an example, a copper overload in liver and brain is the main cause of the Wilson's disease, while a metabolic disorder of Cu(II) can be linked to the Menkes disease. In parallel, iron deficiency leads to anemia and its varying symptoms.

Usually, the transition metal ions are sequestrated by proteins and enzymes. When this is not the case, transition metal ions (such as Fe and Cu) are in their free states and can provoke significant cell damages, particularly *via* the formation of free radicals termed reactive oxygen species (or ROS). The ROS include superoxide anion radical $O_2^{\bullet-}$ and hydroxyl radical $OH^{\bullet}$ and lead to oxidative stress playing prominent roles in the development of several pathologies such as cardiovascular and neurodegenerative diseases or cancers.

In order to counteract the deleterious effects of ROS *in vivo*, living organisms have developed defense strategies involving enzymes, vitamins or proteins which regulate ROS production. Interestingly, at low concentrations, ROS contribute to the proper functioning of the organism and are needed in many vital processes, *e.g.*, in the regulation of gene expression or in the immune defense against pathogens. However, this biological ability to regulate ROS concentration depends on several factors and can be deficient, mainly due to environmental factors including smoking, food, pollution, stress, etc. This explains why the research and development of innovative antioxidants is focusing intense interests. Indeed, new effective antioxidants are expected to decrease the oxidative stress *via* a decrease of the ROS concentration. To design such antioxidants, several strategies can be considered. In this project, it is proposed to prevent the ROS formation interacting with transition metals involved in the Fenton and Haber-Weiss reactions.

OBJECTIVES: ROS are produced from the reduction of molecular oxygen O_2 *via* Fenton and Haber-Weiss reactions. In this process, reductions of O_2 to $O_2^{\bullet-}$ or of H_2O_2 to $OH^{\bullet}$ require a catalyst. Interestingly, these catalysts are transition metal ions *in vivo*, specifically copper and iron. In order to prevent the ROS formation, our strategy consists of the inhibition of the catalysis, *via* a sequestration of these metals. Thus, redox reactions are subsequently jeopardized, decreasing the ROS production.

Based on this context and recent results obtained from our teams, we propose for this postdoctoral fellowship to design, synthesize and study innovative chelators able to interact with Fe(III) and exhibiting antioxidant activities. For the chelators, peptide derivatives have been chosen thanks to their indubitable qualities in terms of biocompatibility, biodegradability and high modularity. The hired postdoc will have in charge the synthesis of a pool of peptide derivatives, the thermodynamic and structural studies of the complexation and then, the evaluation of the antioxidant properties.

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TASKS: The project is comprised of three main tasks:

#1: Synthesis. The peptide derivatives will be synthesized using solid-phase peptide synthesis, purified by reverse-phase HPLC and analyzed by ^{1}H NMR (1D and 2D), high-resolution mass spectrometry and HPLC-MS.

#2: Thermodynamic and structural studies of the complexation. The main part of this project is the study of the ability of the newly synthesized peptides to complex Fe(III). The affinity and the selectivity against other biologically relevant metals will be evaluated, as well as the understanding of the peptide functional groups involved in the complexation which is a key point of this project. To access the thermodynamic and structural parameters, an entire panel of analytical techniques will be carried out, including: UV-vis-NIR, FT-IR, Raman, circular dichroism, spectrofluorimetry, NMR, RPE, potentiometry, SPR and IMAC-MS.

#3: Antioxidant evaluation. Measurement of the ROS concentration can be performed directly (*via* RPE) or indirectly. In this latter case, several assays can be used. For this postdoctoral fellowship, several methods are considered, including ascorbate and nitroblue tetrazolium tests; in parallel, introduction of new antioxidative assays using biological reductants are planned, as well as measurement of hydrogen peroxide *via* a fluorescein derivative (detected by spectrofluorimetry).

SKILLS:

- The candidate should have a Ph.D in chemistry or in bioinorganic chemistry and be trained in coordination chemistry.

- The candidate should have experience in the main analytical and spectroscopic techniques used along this project (potentiometry, UV-vis-NIR, FT-IR, Raman, spectrofluorimetry and/or RPE).

- Knowledge in peptide chemistry and/or antioxidant assays will be an asset.

Scientific contacts: ***STEFAN Loïc (LCPM UMR7375), loic.stefan@univ-lorraine.fr***

SELMECZI Katalin (L2CM UMR7053), katalin.selmeczi@univ-lorraine.fr

TERMS AND TENURE

This position will be based at Laboratoire de Chimie Physique Macromoléculaire LCPM UMR7375 (1 rue Grandville, 54000 NANCY) and Laboratoire Lorrain de Chimie Moléculaire L2CM UMR7053 (Boulevard des Aiguillettes, 54506 VANDOEUVRE-LES-NANCY)

The target start date for the position is ***January/February 2019,*** with some flexibility on the exact start date.

HOW TO APPLY

Applications are only accepted through email. All documents must be sent to loic.stefan@univ-lorraine.fr , katalin.selmeczi@univ-lorraine.fr and aya.khanji@univ-lorraine.fr

Deadline for application is December 14th, 2018.

JOB LOCATION

Nancy, Lorraine, France

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REQUIREMENTS

Applicants are requested to submit the following materials:

- A cover letter applying for the position
- Full CV, including academic records and list of publications
- Statement of Research
- Two Letters of recommendations