DOCTORAL FELLOWSHIP

OPEN POSITION

Novel organoselenium coumpounds: From the heart of the tuna fish to antioxidant capacity via intricate nitric oxide signaling - SeleNOx

PHD SUPERVISORS

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DESCRIPTION

In recent years, a particular interest has been given to organoselenium compounds as antioxidants, regulating free radical reactions in the organism, and mimicking glutathione peroxidase (GPx) activity[1-4]. In contrast to popular opinion, organoselenium compounds are not "artificial" or alien to Biology. They are often "natural", found, for instance, as selenoneine, the major form of organic selenium in tuna[5], or as selenoproteins, such as the GPx family and the thioredoxin reductase (TrxR) in mammals[6,7]. Indeed, in selenoproteins, the selenocysteine residue with a selenol (–SeH) group exhibits superior redox properties compared to the thiol group of the cysteine residue[8]. This activity has been mimicked by small molecule catalysts, and ebselen, the flagship organoselenium-based mimic, exhibits moderate GPx-like catalytic activity attributed to thiol exchange reactions, which protects thiol groups of proteins from oxidation. Even if ebselen shows low solubility in aqueous medium - hence generally limiting pharmaceutical applications - it is currently being investigated in clinical trials for Meniere's disease (Phase 2, US) and for bipolar disorder (Phase 2, UK). From a physiological perspective, the interaction of selenium with nitric oxide (NO) is particularly stimulating. Ebselen derivatives have been used as a cover of medical devices to release NO from blood circulating S-nitrosothiols (RSNOs) in the presence of cysteine[9]. NO released from this type of catalysis shows antithrombotic properties. Indeed, NO is an endogenous radical implicated into vascular homeostasis, responsible for antithrombotic properties to vasodilation. RSNOs, such as S-nitrosoglutathione (GSNO), are the main storage forms of this highly reactive gasotransmitter in tissues[10]. We recently demonstrated that NO released from GSNO protects cysteine residues of proteins from oxidation in vascular smooth muscle cells[11].

Since both, selenium compounds and NO-releasing agents, seem to protect cysteine residues, a joint action of these two prominent "antioxidants" may be particularly effective. The aim of this project therefore is to develop such "double impact" molecules which combine the catalysis of selenium with NO release, and hence counteract vascular oxidative stress particularly efficiently. From a chemical perspective, such small molecule organoselenium compounds are not only feasible and may indeed be modelled on naturally occurring selenonine, they may also provide additional benefits, such as higher aqueous solubility and GPx-activity than ebselen. Indeed, the redox-modulating thiol exchange properties of these selenoderivatives will be employed to stimulate the release of NO from physiological RSNOs. In this perspective, the organoselenium compounds developed as part of this project could counteract oxidative stress and restore the NO pool, which both are highly beneficial events in cardiovascular disease and, in the medium term, could promote the therapeutic applications of these drug candidates in association with RSNOs.

AIMS AND METHODS

The programme is designed to provide expert multidisciplinary training in synthetic chemistry and in biology, in two phases and at two sites within the UGR. In the first phase, the PhD student, with the help of C. JACOB (Professor) and Y NEY, A KHARMA (senior PhD students) will synthesize

and, by physico-chemical analytical techniques characterize a range of around ten new organoselenium compounds. These compounds will be designed to be stable and soluble in a physiological environment. They will become activated in the presence of certain biomolecules, such as GSH. To verify independently the antioxidant power of these molecules, cyclic voltammetry experiments and antioxidant assays, such as the 2,2-diphenyl-1-picrylhydrazyl assay (DPPH)[12], the FRAP assay and the Total Antioxidant Capacity Assay (TAC) will be carried out. The catalytic properties will be established in a GPx-assay based on hydrogen peroxide and thiophenol. The resulting selenium species will not only be redox-catalytic, they will also be highly nucleophilic and hence able to release NO from a range of carriers. Such Reactive Selenium Species will also exhibit their own pharmacological profiles once placed inside cells, and this can be studied with the assistance of "intracellular diagnostics"[13]. Together, the Division of Bioorganic Chemistry therefore will provide complementary experience, expertise, techniques and studies in the field of isolation, characterization, synthesis and analysis of agents, from natural products to complicated 77Se-NMR, electrochemistry, initial biological assays and FACS analysis as part of mode of action studies. Besides these important and central methods, the platform for "intracellular diagnostics" and various methods for nanosizing will also be available[14,15].

In the second phase, the PhD student will move to the UL. Here, and with the help of C. Gaucher (associate professor) and C. Perrin-Sarrado (associate professor), she/he will evaluate the GPx-like activity of each organoselenium compound synthesized in the presence of various oxidants and thiols. The most promising compounds will be evaluated in the in vitro model of oxidative stress induced by a radical generator on vascular smooth muscle cells[11]. This model showed a decrease of intracellular reduced thiol concentrations, as well as glutathione efflux and modifications of redox enzymes activity. Subsequently, the ability of organoselenium compounds to release NO from RSNO in the presence of a reducing agent will be evaluated using NO quantification methods already established by the French partner. The panel of intracellular *S*-nitrosated proteins will be identified to consider new pharmacological targets of NO. The most promising compounds will be evaluated for vaso-relaxing properties on rat aortic rings using an aorta bench available in the laboratory of the French partner. First, the potentialization of NO release from RSNO by selenocompounds will be translated in effective concentration 50 (EC_{50}) and Emax values. Next, as the French partner already showed that RSNO can achieve the formation of a NO store within the vascular wall, the potentiality of selenocoumpounds to mobilize this NO store will be studied along vasorelaxation.

PROJECT SCHEDULE

The applicant will be involved in:

- Synthesis and comprehensive characterization of selenocompounds, acellular redox and catalytic assays, antioxidant capacities and NO release from RSNO
- *In vitro* antioxidant capacity of selenocompounds in a cell model of oxidative stress, NO release and storage in cells and tissues, *S*-nitrosation of proteins and enzymes
- Pharmaceutical activity of selenocompounds, vasorelaxant properties and mobilization of the vascular NO store
- The applicant will spent half of the time within the facilities of the German partner in Saarbruecken and the other half of the time within the facilities of the French partner in Nancy.

REFERENCES

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JOB LOCATION AND TERMS

This position will be based at the « Cibles thérapeutiques et expertise préclinique du médicament (CITHEFOR) » EA 3452, Université de Lorraine, Brabois-Health campus, Vandoeuvre-les-Nancy, France, and the Division of Bioorganic Chemistry, School of Pharmacy, Saarland University, Germany. Under this special co-tutelle arrangement, the studies will result in an international PhD degree awarded jointly from both partner Universities. The duration cannot exceed 36 months.

The target start date for the position is ***September or October 2019***.

HOW TO APPLY

Applications are only accepted through email. All document must be sent caroline.gaucher@univ-lorraine.fr and c.jacob@mx.uni-saarland.de
Deadline for applications is ***April 30, 2019***. Applicants will be **interviewed by an Ad Hoc Commission by *June 15, 2019*.**

REQUIREMENTS

The successful PhD applicant has a strong background in Pharmacy, enabling a complete and successful investigation conducted as part of this pluri-disciplinary research project, which involves synthetic and analytical chemistry, cell biology, molecular biology, and also pharmacology. The applicant should hold a Master degree with higher than average marks of 12/20 in M2 (for French applicants), 2.3 (for German applicants), an upper second for UK applicants, or otherwise ranking in the first third of the respective national marking scheme. The applicant should be motivated to spend time in different countries and scientific disciplines, and therefore should be able to communicate in (basic) French, German and English, although relevant language courses will be provided during the project

Applicants are requested to submit the following documents:

- Letter of Motivation and CV
- Transcripts of all marks of the Master degree (first and second year) with the certificate of success (if already available)
- Two recent letters of recommendation
- A detailed description of the subjects of your last year as trainee