**Post-doctoral position available**

Employer: CNRS
Contract: CDD
Place of work: BIG, CEA-Grenoble, Rhône-Alpes, France
Salary: ~2000-2200 € / month

The Laboratory of Chemistry and Biology of Metals (LCBM) is a mixed laboratory (CEA, CNRS, Grenoble Alps University) that takes part of the BIG institute at the CEA of Grenoble. The laboratory, at the interface between chemistry and biology, focuses on the study of the structure, activity and regulation of complex biological systems using or transporting metals.

A 2 years post-doctoral fellowship is available in the "Biocatalysis" team (headed by S. Ollagnier de Choudens) of the LCBM that works on the assembly and reactivity of iron-sulfur proteins, involving chemists, biochemists and biologists. The project is financed by the French "Agence Nationale de la Recherche" (ANR).

**Summary of the project:**

**Background**. Nicotinamide adenine dinucleotide (NAD) plays a crucial role as a cofactor in numerous essential redox biological reactions. In fact, in all living organisms, NAD derives from quinolinic acid, the biosynthetic pathway of which differs among organisms. In most eukaryotes, quinolinic acid is produced via the degradation of tryptophan. Alternatively, in bacteria, quinolinic acid is synthesized via a unique condensation reaction between iminoaspartate and dihydroxyacetone phosphate (DHAP)[1]. This reaction is catalyzed by quinolinate synthase, encoded by the *nadA* gene. Besides the *de novo* synthesis of NAD, a salvage pathway may exist that enables it to be recycled from diverse metabolites. *Mycobacterium leprae* and *Helicobacter pylori*, pathogens causing leprosy and certain stomach cancers, respectively, lack a salvage pathway, which unables them to recycle NAD and are thus strictly dependent on the iminoaspartate-DHAP pathway. The presence of different pathways for the biosynthesis of quinolinic acid in most prokaryotes and eukaryotes, in addition to the absence of the salvage pathway in some microorganisms, make NadA a target for the development of new specific antibacterial drugs. NadA is a universal metalloenzyme containing an $Fe_4S_4$ cluster essential for catalysis[2-4]. During the last years (ANR NADBIO), we solved the crystal structure of NadA with its Fe/S cluster, demonstrated the role of the cluster during catalysis and partially unravel the molecular mechanism of the reaction catalyzed by NadA[5-8]. In the context of a new ANR contract (NADIN project 2017-2019) our goal on the NadA system is to identify inhibitors of NadA as antibacterial agents directed against *H. pylori* and *M. leprae*.

**Post-doc project**. To identify inhibitors of NadA, we will use three strategies (i) the design of synthetic molecules based on the first inhibitor that we made in 2012[5] and the recent NadA structural crystallographic data[6,8], (ii) the virtual screening of compounds using molecular docking with two NadA structures as targets and (iii) the use of high-through screening (HTS) with NadA both *in vitro* and *in vivo*. The candidate for the Biocatalysis team (CEA Grenoble) will have to assay and characterize *in vitro* inhibitors that will be identified and perform HTS experiments. As a consequence, he/she should have a strong expertise in biochemistry, a good background in enzymology and an interest for structural biology. Candidates should preferably have defended their PhD in the last 2 years.
Applications should be sent to Sandrine Ollagnier (sollagnier@cea.fr).

**References**


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3. Cicchillo, R.M. et al. Escherichia coli quinolinate synthetase does indeed harbor a [4Fe-4S] cluster. *J Am Chem Soc* **127**, 7310-1 (2005).
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5. Chan, A. et al. Studies of inhibitor binding to the [4Fe-4S] cluster of quinolinate synthase. *Angew Chem Int Ed Engl* **51**, 7711-4 (2012).
6. Cherrier, M.V. et al. The crystal structure of Fe(4)S(4) quinolinate synthase unravels an enzymatic dehydration mechanism that uses tyrosine and a hydrolase-type triad. *J Am Chem Soc* **136**, 5253-6 (2014).
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