Development of a nuclearised instrumental platform and associated methods to analyse actinide-peptide species of interest in nuclear toxicology

Understanding and limiting the impact of actinides (An) generated by research and industry on man is a major issue. In this sense, the knowledge of the affinity of An for their target proteins could help to better understand the mechanisms of An toxicity. The study of complexing properties towards An, of series of peptides mimicking these target proteins, is a promising way to identify the key parameters behind this affinity and to suggest specific coordination sites of An in proteins, yet unknown. These data are also essential to develop new highly selective decorporating agents.

In this project, a nuclearised instrumental platform will be developed in a laboratory dedicated to the handling of radioactive samples, to determine the affinity scale of biomimetic peptides for An (Pu, Am, Cm…) in a single analysis. Since the samples will be mixtures of An-peptide species at the trace level, the strategy relies on the setting up of the simultaneous coupling of the separation of these species by hydrophilic interaction chromatography (HILIC), to electrospray mass spectrometry (ESIMS) and to inductively coupled plasma mass spectrometry (ICPMS). The feasibility of the simultaneous coupling has been previously demonstrated by the host laboratory in non-nuclearised conditions.

The candidate will be responsible for the adaptation of the simultaneous HILIC-ESIMS/ICPMS coupling to nuclearised instruments, taking into account the constraints of the glove boxes as well as the technical characteristics of each instrument. The project focuses on the implementation into glove boxes of a nuclearisable ESI-MS and the associated chromatographic devices, as well as the coupling of this assembly to an ICP-MS, already nuclearised. The development of this instrumental platform requires several technical modifications, such as the adaptation of the ionisation sources to the nuclearisation interface, the design of specific interfaces dedicated to electrical connections and the supply of the fluids and able to cross the panel of the glove boxes, the autosampler modifications which must allow its remote control etc. This nuclearisation step will be validated by the analysis of known samples.

Afterwards, the analytical developments related to the separation conditions of the An-peptide species by HILIC, the structural characterization of the species by ESI-MS as well as the elemental and isotopic characterization of the An by ICP-MS, will be carried out. The quantitative distribution of the An thus determined in each species through this integrated approach, will allow to establish an affinity scale in a single analysis. Following the same approach, the selectivity of the peptides with the highest affinity will be evaluated towards endogenous competing ions (Ca^{2+}, Cu^{2+}, Zn^{2+}, Fe^{3+}), in the presence of the An.

This post-doctoral project (12 months with extension) will be led in collaboration between two laboratories:

- LANIE (Laboratoire de développement Analytique Nucléaire, Isotopique et Elémentaire) : host laboratory
  Département de Physico-Chimie - Service d'Etudes Analytiques et de Réactivité des Surfaces
  Commissariat à l'Energie Atomique et aux Energies Alternatives - Direction de l'Energie Nucléaire - Centre de Saclay

Commissariat à l'énergie atomique et aux énergies alternatives
Centre de Saclay – F 91191 Gif-sur-Yvette Cedex

DEN/DANS/DPC/SEARS/LANIE - Bât. 391 - PC 33
Tél : +33 (0) 1 69 08 26 59 thomas.vercouter@cea.fr
Secrétariat : +33 (0) 1 69 08 79 09 - Fax : + 33 (0) 1 69 08 94 75

Direction de l'énergie nucléaire
Direction des activités nucléaires de Saclay
Département de physico-chimie
Service d'études analytiques et de réactivité des surfaces
Laboratoire de développement analytique nucléaire, isotopique et élémentaire

- CIBEST (Chimie Interface Biologie pour la Santé l'Environnement et la Toxicologie) : design and synthesis of series of peptides mimicking protein binding-sites with high affinity for actinides.
  Systèmes Moléculaires et nanoMatériaux pour l'Energie et la Santé (SyMMES), UMR 5819 CEA – CNRS – UGA, INAC
  Commissariat à l'Energie Atomique et aux Energies Alternatives – Direction de le Recherche Fondamentale - Centre de Grenoble

The candidate will benefit from state of the art analytical instruments, in conventional laboratory but also in the laboratory dedicated to the analysis of radioactive samples, as well as from the skills and the experience of the LANIE members in the field of the nuclearisation of instruments, speciation analysis, the coupling of separation techniques with different mass spectrometers, transient signal treatment and high precision elemental and isotopic analyses. She/he will also benefit from the competences of the CIBEST, in the field of biomimetic chemistry, the design and the synthesis of peptides dedicated to chelation of metals.
The skills and the experience acquired by the candidate during this post-doctoral project will be greatly valuable for her/his professional project. She/he will be able to extend her/his knowledges to the study of the interaction of numerous elements/metals with various organic ligands for various applications, such as impact evaluation of radionuclides/highly toxic metals on humans and environment, speciation analysis of elements in complex mixtures, the development of treatment processes for the recycling of strategic metals or spent nuclear fuels…

Required profile:
PhD in the field of instrumentation and analytical chemistry, with a strong background in the coupling of chromatographic techniques with different mass spectrometers. Skills in glove box handling will be valuable.
The candidate will be in charge of the project management, covering the nuclearisation of the instruments, the setting up of analytical developments with nuclearised instruments, in interaction with the members of the LANIE, the CIBEST and the different companies, the synthesis, the interpretation and the reporting of the results as well as their valorisation through communications and publications. The applicant is expected to be autonomous and innovative, to demonstrate ability to write, communicate and work in an interdisciplinary approach.

Starting date:
First quarter of 2019 – CEA Saclay center, 20 km near Paris

Contacts:
To apply, send an email with detailed CV, list of publications, and motivation letter to
carole.bresson@cea.fr, DPC/SEARS/LANIE, CEA Saclay - Phone: +33 1.69.08.83.48
pascale.delangle@cea.fr, CIBEST, SyMMES, UMR 5819 CEA – CNRS – UGA, INAC, CEA Grenoble - phone : +33 4 38.78.98.22

References
1 : M. Starck, F. A. Laporte, S. Oros, N. Sisommay, V. Gathu, P. L. Solari, G. Creff, J. Roques, C. Den Auwer, C. Lebrun, P. Delangle, Chemistry – A European Journal 23 (2017) 5281.
2 : C. Lebrun, M. Starck, V. Gathu, Y. Chenavier, P. Delangle, Chemistry – A European Journal 20 (2014) 16566.
3 : L. Beuvier, C. Bresson, A. Nonell, L. Vio, N. Henry, V. Pichon, F. Chartier, RSC Advances 5 (2015) 92858.
4 : E. Paredes, E. Avazeri, V. Malard, C. Vidaud, P. E. Reiller, R. Ortega, A. Nonell, H. Isnard, F. Chartier, C. Bresson, Proceedings of the National Academy of Sciences of the United States of America 113 (2016) 14007.
5 : E. Paredes, E. Avazeri, V. Malard, C. Vidaud, R. Ortega, A. Nonell, H. Isnard, F. Chartier, C. Bresson, Talanta 178 (2018) 894