Postdoctoral position in peptide & protein chemistry

Topic: ***New methodologies for Pd-catalyzed conjugation of peptides and proteins***
Duration: 18 months
When: Starting date is scheduled to May or June 2023
Where: Centre de Biophysique Moléculaire, UPR CNRS 4301, Orléans, France
Supervisor: Dr Vincent Aucagne, team "Synthetic Proteins and Bioorthogonal Chemistry"
Deadline for the submission of an application: March 21st, 2023

Context

Chemical modification of peptides and proteins is an important technique for probing natural systems, creating therapeutic conjugates and generating novel protein constructs. Site-selective reactions require control over both chemo- and regioselectivity, at room temperature and under aqueous conditions. Many methods have been developed for achieving modification of proteins but unarguably, the most widely used site-selective bioconjugation reactions are the series of thio-crosslinking reactions between the nucleophilic thiol group of a cysteine residue and a variety of electrophiles. Thiyl radical can also be utilized for bioconjugation through thiol-ene coupling chemistry. Whilst these approaches offer advances in the growing field of peptides and proteins bioconjugation, they suffer from some drawbacks. Thus, the development of novel methods for site-selective functionalization of unprotected peptides and proteins under mild conditions is highly desirable.

Project aims

The national research agency-funded "ThioFUN" project combines the expertise of three teams of chemists (Vincent Aucagne – CNRS Orléans, Samir Messaoudi – Université Paris Saclay, David Audisio – CEA SAclay). It focuses on the development of a Pd-catalyzed technique for a site-specific thioconjugation of peptides or proteins with various thiol nucleophiles, under conditions compatible with the most sensitive proteins. The centerpiece of this strategy is based on the "tag-and-modify" approach, which entails sequential installation of *p*-iodophenylalanine (pIPhe) as a uniquely reactive chemical group into the protein (the electrophilic "tag", totally unreactive in the absence of catalyst) and the selective and specific modification of this group with diverse thiols. Developing such a method that can generate a non-labile C(sp2)–S bond more stable than the C(sp3)–S bonds formed in most previously reported reactions would be a major advance in the field of bioconjugation chemistry.

The recruited postdoc will be in charge of designing and conducting research experiments, analyze relative data and interpreting results. He/She will summarize relevant scientific literature on the latest developments of thio-conjugation, contribute in writing scientific papers based on their research findings, present their research findings at meetings involving the other ANR partners, at national and international conferences, and work closely with the other members of the research group.

Host laboratory

Founded in 1967, CBM fosters interdisciplinary collaborations between chemists, biologists and biophysicists. Our research focuses on the understanding of the role and the mechanisms of action of biomacromolecules, using and developing techniques from structural, molecular and cellular biology, biomedical imaging, synthetic chemistry and chemical biology. The presence of a broad range of large instrumentation dedicated to these multidisciplinary research areas is another significant characteristic of the center.

Candidate profile

The candidate should be a synthetic chemist with excellent skills in synthesis, purification and use of state-of-the-art HPLC, MS and NMR. Previous experience in solid-phase synthesis and peptide and protein science will be advantageous. He/she should be highly motivated, rigorous, have a strong interest in the chemistry/biology interface and show his/her capacity to work independently and as part of a team made of researchers and engineers from different fields.

Application submission

Candidates for this position should submit by email a cover letter, CV and contact details for at least two letters of reference. **Deadline: March 21st 2023**.
Contact: Vincent Aucagne – aucagne@cnrs-orleans.fr – 02 38 25 55 77.

Selected publications of the team related to the project

Montoir *et al.* Synthesis of Aryl-Thioglycopeptides Through Chemoselective Pd-Mediated Conjugation, *Chem. Sci.*, 2018, *9*, 8753−8759.

Abboud *et al.* Enzyme-cleavable linkers for protein chemical synthesis through solid-phase ligations, *Angew. Chem. Int. Ed.*, 2021, *60*, 18612−18618.

Abboud *et al.* A straightforward methodology to overcome solubility challenges for N-terminal cysteinyl segments in native chemical ligation, *Chem. Sci.*, 2021, *12*, 3194−3201.

Jacobsen *et al.* A helping hand to overcome solubility challenges in chemical protein synthesis. *J. Am. Chem. Soc.*, 2016, *138*, 11775−11782.

Terrier *et al.* A straightforward method for automated Fmoc-based synthesis of bio-inspired peptide crypto-thioesters. *Chem. Sci.*, 2016, *7*, 339−345.

Galibert *et al.* Combining triazole ligation and enzymatic glycosylation on solid phase simplifies the synthesis of very long glycoprotein analogues. *Chem. Sci.*, 2015, *6*, 3617−3623.

Aucagne *et al.* Towards the simplification of protein synthesis: iterative solid-supported ligations with concomitant purifications. *Angew. Chem. Int. Ed.* 2012, *51*, 11320-11324

Valverde *et al.* Synthesis of a biologically active triazole-containing analogue of cystatin A through successive peptidomimetic alkyne–azide ligations. *Angew. Chem. Int. Ed.* 2012, *51*, 718-722.