CYCLE DE CONFÉRENCES DE CHIMIE

Avec le concours de : Université Clermont Auvergne
INP Clermont Auvergne

Jeudi 16 octobre à 16 h

Amphi Rémi (site des Cézeaux)

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Inventing tools for simplifying chemical protein synthesis

Chemical synthesis of proteins emerged in the past decades as an alternative to recombinant techniques for applications including the elucidation of biological mechanisms at the molecular level, drug discovery and synthetic biology. Such an approach is particularly appealing for accessing homogeneous and well-characterized site-specifically modified small proteins (typically 60-200 amino-acids (aa)-long) which are difficult or impossible to obtain through biotechnology, and overcome the limits of solid-phase peptide synthesis (SPPS) in terms of peptide sequence length.

Current techniques focus on the controlled assembly of smaller, unprotected peptide segments either synthesized by SPPS or obtained through recombinant means, through highly selective "chemical ligation" reactions in aqueous buffers. This approach revolutionized the field some thirty years ago and is gradually being democratized for the synthesis of small proteins (60-100 aa). However, access to more ambitious targets in terms of size or molecular complexity is often a *tour de force* still reserved for rare specialists, and with considerable efforts. Three major bottlenecks still remain to be overcome: (1) the assembly of multiple fragments by successive ligations, that requires repeated purification steps ultimately leading to very low overall yields, (2) the handling of poorly soluble or aggregation-prone segments, which is an extremely common problem when dealing with a given protein sequence, and (3) the development of alternative reacting groups for existing chemical ligation reactions, as well as alternative reactions.

The main focus of our research group relies on the chemistry-driven conception and development of original methodologies to overtake these limitations. Our primary goal is thus to build a robust and versatile molecular toolbox aimed at simplifying the access to medium-sized proteins. A second major research axis is devoted to biology-driven applications, in close collaboration with biologist colleagues, through the synthesis of small proteins difficult to access through recombinant techniques. These include disulfide-rich small proteins that necessitate the controlled formation of multiple SS bonds, proteins incorporating reporting probes, or tailored-made modifications to provide resistance to enzymes such as specific proteases.

[1] E. H. Cisse and V. Aucagne, *Chem. Sci.* **2025**, *16*, 11496.
[2] S. A. Abboud *et al.*, *Angew. Chem. Int. Ed.*, **2021**, *60*, 18612−18618.
[3] S. A. Abboud *et al.*, *Chem. Sci.*, **2021**, *12*, 3194−3201.
[4] V. P. Terrier *et al.*, *Chem. Sci.*, **2016**, *7*, 339−345.
[5] M. T. Jacobsen *et al.*, *J. Am. Chem. Soc.*, **2016**, 138, 11775−11782.
[6] V. Aucagne *et al.*, *Angew. Chem. Int. Ed.* **2012**, *51*, 11320−11324.
[7] I. Valverde *et al.*, *Angew. Chem. Int. Ed.* **2012**, *51*, 718−722.

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