De novo peptides for the development of artificial metalloenzymes

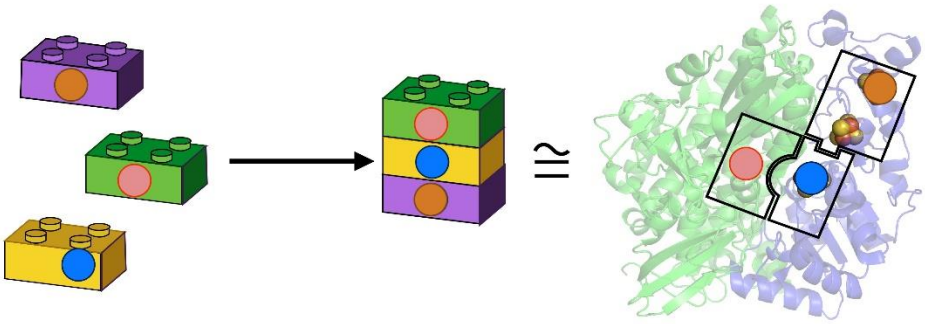
Keywords. Peptide design & synthesis, self-assembly, amyloid-like fibril, artificial metalloenzyme.

Context. Catalyzing chemical reactions (including those not observed in nature) in mild conditions and with high regio- and enantio-selectivities is challenging, but is highly important for future industrial development (pharmaceutical, in particular). The field of artificial metalloenzymes (ArMs) is growing because it tackles this challenge by combining the catalytic properties of abundant metals and proteins in order to perform relevant (fundamental and applied) reactions.[1] Even though the strategies developed so far have already achieved impressive results, very few ArMs are based on a scaffold developed by rational design.

In addition, nature often uses the combination of several proteins in a complex to achieve difficult chemical processes (N_2 reduction, H_2 production, ATP synthesis — not to mention the photosystems). In such systems, several sites act in combination (eg catalytic sites, electron transfer centers), and their positioning (the distance between them) is a key parameter for the efficiency of the process, as exemplified by the group of Utschig recently.[2,3]

Developing multisite ArMs is currently very difficult, and examples are scarce. To date, ArMs are based either on a natural protein scaffold or on a *de novo* peptide. In both strategies, the rational design of a complex system — containing several reactive sites in close vicinity — is difficult. For this, the use of one folded protein is limited since multiple covalent functionalizations could impact the folding, and non-covalent approaches are often not site-specific. In the approach based on *de novo* peptides, supporting two sites on one scaffold is delicate due to their small size and related structural disturbance.

Project description. This project proposes a new approach that could overcome some of these current limitations: to develop a methodology for the construction of multi-sites ArMs based on the controlled assembly of small *de novo* peptidic bricks (“molecular Lego”, see scheme). The bricks are accessible by peptide synthesis, rendering their functionalization at a single site straightforward. Upon assembly of several units, a more complex structure (protein-like) will be obtained, placing the different functional centers at a desired distance to work in concert. One could then rationally design complex ArMs simply by assembling those bricks. To our knowledge, no such system exists yet.



During this PhD, we will design, synthesize and characterize these “peptidic bricks”. They will be then modified in order to optimize and control their self-assembly. Finally, the scaffold will be functionalized to bind metal ions and perform catalysis (proof-of-concept of an ArMs built by assembling these bricks).

In practice, the project involves the synthesis of several peptides (by solid phase peptide synthesis followed by HPLC purification), and the test of their ability to assemble (formation of fibers or soluble multimers) and to fold properly. Then, the assemblies will be characterized by spectroscopic means (CD, NMR, DLS, IR), as well as microscopies for the fibers (TEM, SEM, AFM).

Profile. The candidate must have a master degree, or equivalent, with a major in Chemistry. Knowledge and experience in synthesis, supramolecular chemistry or chemistry at the interface with biology (eg protein/peptide synthesis, artificial enzymes, enzymatic catalysis, chemical biology) or materials (eg nanotechnology, soft materials) would be a plus. Given that it will be at the frontiers with several disciplines, a high motivation and ability to learn new fundamental knowledge and technics is important.

Language. Speaking French is not mandatory, English is enough. Whatever nationality of the candidate, good skills in English (written and spoken) will be highly appreciated.

Duration. 36 months, starting from October 2019 (or September if candidate prefers).

Funding & supervision. This PhD position is funded by the ANR contract *LeBHel-AMzymes*. Monthly salary will be c.a. 1 378 netto, after taxes. This PhD thesis will be co-supervised by Vincent Lebrun (research associate, CNRS) and Peter Faller (Professor, Université de Strasbourg) in the UMR 7177, Institut Le Bel.

To know more about our group, please visit our website : https://bcb.chimie.unistra.fr

Application process. Applications must be sent to Vincent Lebrun (vlebrun@unistra.fr), before April the 30th 2019. A cover letter showcasing the motivation of the candidate and a CV, including two references that we can contact, are required. After a first selection of folder, interviews will be performed, onsite or via skype, second week of May.

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[2] S. R. Soltau, J. Niklas, P. D. Dahlberg, O. G. Poluektov, D. M. Tiede, K. L. Mulfort, L. M. Utschig, *Chem. Commun.* **2015**, *51*, 10628–10631.

[3] S. R. Soltau, P. D. Dahlberg, J. Niklas, O. G. Poluektov, K. L. Mulfort, L. M. Utschig, *Chem. Sci.* **2016**, *7*, 7068–7078.