Master 2 Internship Offer

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Team F « Alzheimer et amyloïdes : bases moléculaires, thérapie par chélation and détection » et Teame K ***«*** *Agents anti-Infectieux moléculaires et macromoléculaires* ***»***
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Synthesis and evaluation of a Peptide-Metalloporphyrin conjugate in a bio-inspired catalysis approach

Amyloid peptides have particular aggregation properties that induce their self-assembling as high-ordered and insoluble three-dimensional structures called "amyloid aggregates" (Figure 1A). **Thus, amyloid peptides are of particular interest for the development of new approaches in the field of bio-inspired and supported catalysis** (*Coord. Chem. Rev. 2016, 308, 445-459*). The fibrillar structure adopted by aggregated amyloid peptides and the robustness of the corresponding buildings make possible considering their supramolecular assemblies as platforms for hosting metal centers for applications in heterogeneous catalysis. Moreover, such three-dimensional structures integrating a metallic catalytic site have surfaces and/or confinement pockets whose respective physico-chemical properties may be suitable for modulating the reactivity and specificity of catalyzed reactions. Various strategies can be considered to insert a catalytic metal center onto an amyloid aggregate and thus develop a new artificial metallo-enzyme. Such an insertion can be obtained (i) by complexation of a metal ion by some amino acids of the primary structure of the amyloid peptide, (ii) by supramolecular interaction of a catalytic complex with the amyloid aggregate, (iii) by covalent conjugation of a metal complex with the amyloid peptide (***Figure 1B***).

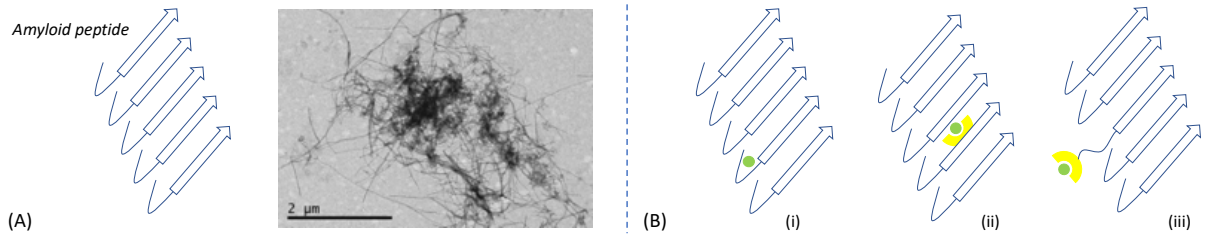

Figure 1. *(A) Schematic representation of a fibrillar amyloid aggregate, composed of n amyloid peptides in intermolecular beta-sheet interactions and TEM image of aggregates composed of Beta-Amyloid peptide. (B) Different modes of insertion of a catalytic metal center into an amyloid aggregate.*

The objective of the proposed internship is to synthesize and characterize a manganese porphyrin - amyloid peptide conjugate for the development of a supported catalyst from the third class (iii) (***Figure 2***). The synthesis of this bioconjugate will be initiated by solid phase peptide synthesis (SPPS) of an amyloidogenic fragment derived from the aggregating unit KLVFF (*Biochemistry 2008, 47, 4597-4605*). The coupling of the manganese metalloporphyrin to this peptide will then be the subject of a methodological study to determine the best conjugation conditions to be applied: (i) on a solid support or in solution, (ii) various conjugation points (N-terminal and/or intra-sequence) will also be considered. The resulting conjugate will be characterized by NMR, HPLC and mass spectrometry. It will then be subjected to a physico-chemical study (fluorescence spectrometry, TEM microscopy) of its aggregation capacities in order to evaluate the conditions to be applied to obtain a supported catalyst of the carbamazepine (CBZ) epoxidation reaction. *This latter part would be subject to preliminary trials if the central phase of the project to produce the targeted peptide conjugate in sufficient quantities for its study is enough advanced.*

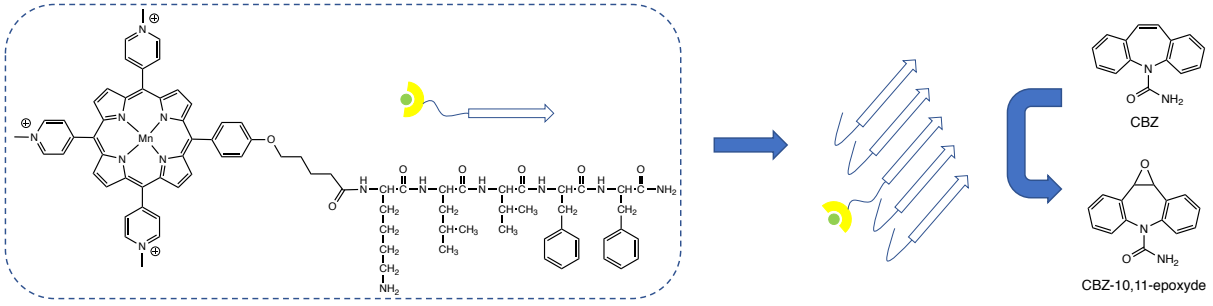

Figure 2. *Structure of the targeted peptide-metalloporphyrin conjugate for the catalysis of the epoxidation of carbamazepine (CBZ).*