PhD supervisors : Dr. Sébastien Blanchard (IPCM) & Pr. Nicolas Giraud (LCBPT)

# Studying the interaction between Polyoxometalates and Amyloid peptides in the context of Alzheimer's disease and Diabetes

This doctoral project, in the framework of ANR SUPRAMY, aims at studying by various physicochemical techniques the nature (location, involved aminoacids, type of bonding, …) of the interaction of amyloids-forming peptides with diverse families of PolyOxoMetalates (POMs) with various charges, shape, etc ...

## Candidate's profile

SUPRAMY is a multidisciplinary project with a strong physicochemistry aspect. The PhD candidate should have a solid formation in chemistry. Interest toward the biological and supramolecular chemistry interface and spectroscopies, in particular NMR, will be strongly appreciated. Applications, including a CV, transcript of master degree, motivation letter and a recommendation letter from the master 2's internship supervisor, should be sent to Sébastien Blanchard and Nicolas Giraud.

## Context of the work

The underlying mechanisms of Alzheimer's disease (AD) and Type II Diabetes Mellitus (T2DM) are not clear, but the extracellular accumulation of the amyloid-β peptides (Aβ) and the Islet Amyloid PolyPeptide (IAPP), respectively, is linked to the onset of the pathologies.[1]

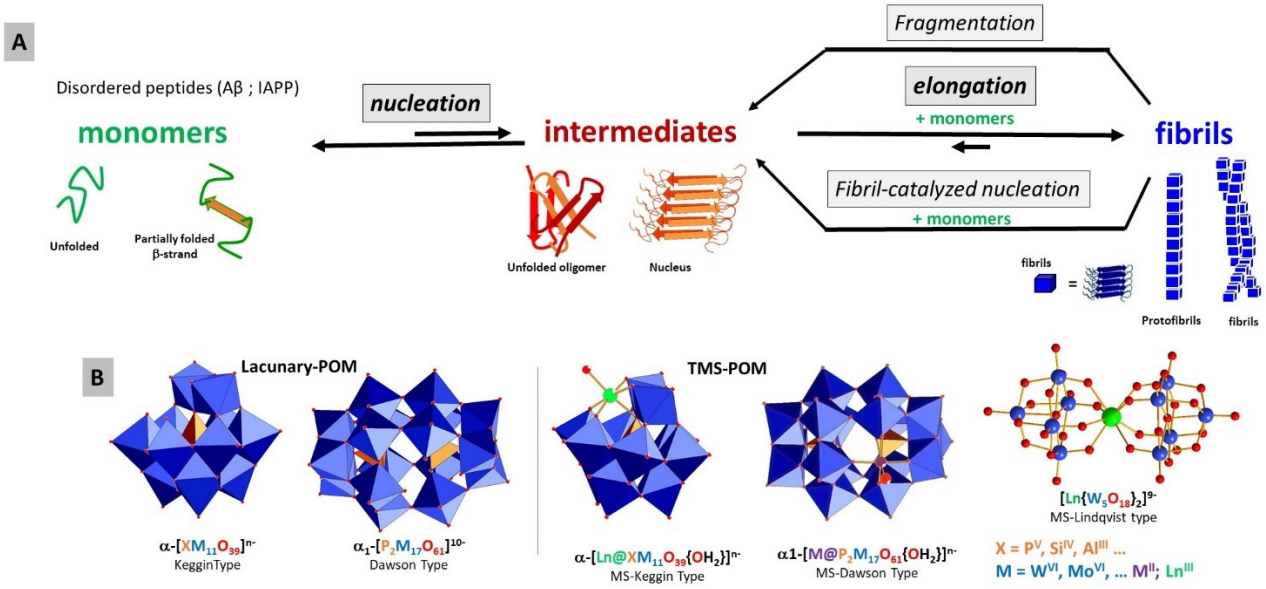


Figure 1. Various phases of fibril formation (complex process) and a few families of POMs that will be studied.

Both Aβ and IAPP peptide's self-assembly lead to intermediates of various sizes, shapes and toxicity.[2] Once an appropriate conformation is taken, monomer associate to form nuclei that grow initially into soluble intermediates before further elongation at their extremities leads to protofibrils. Such protofibrils can associate laterally into fibrils (Figure 1.A).[3] These steps are known as primary nucleation, elongation and maturation. The end species are amyloids, id est cross-β sheets architectures of about 10 nm in diameters and about 100 µm in lengths, corresponding to peptides in their most thermodynamic favourable state. The aggregation process is quite complex, all the more so with fibrils being able to catalyse the nucleation or fragmentate to regenerate oligomers.


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Polyoxometalates (**POMs**) are assembly of ($MO_x$) polyhedra, (M= W(VI), Mo(VI), V(V), ...), in some cases templated by other oxoanions ($XO_y$) (X= P(V), Si(IV), Al(III),..) leading to soluble oxides of general formula $[X_nM_mO_p]^{n-}$. They present a large diversity in size, shape, charge and properties (Figure 1. B).[4] Basic degradation of complete POMs leads to lacunary POMs where one or several $MO^{n+}$ fragments have been removed: these are usually stable at physiological pH, and can also act as all inorganic ligands. Several POMs, either as molecular species or imbedded into nanomaterials, have been reported recently to modulate Aβ peptide self-assembly in vitro and in vivo.[5,6] However, in most cases, little information about the mechanism of POM-peptides interaction is given, especially at the (supra-)molecular scale.

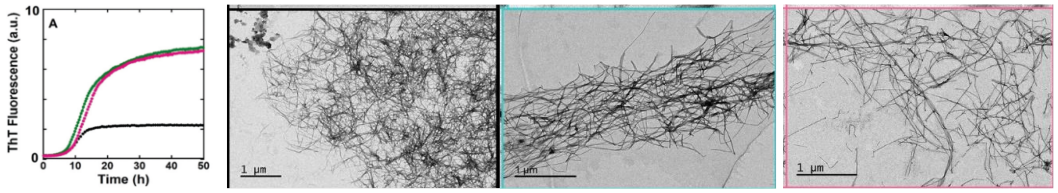


**Figure 2. Effect of POM on the self-assembly of Aβ$_{1-40}$.** ThT fluorescence-monitoring of Aβ$_{1-40}$ self-assembly in the absence (black) or presence of 1 eq. of $K_4[SiW_{12}O_{40}]$ (green) and $K_8[SiW_{11}O_{40}]$ (green), corresponding TEM pictures.[7]

Preliminary results (collaboration Dr. C. Hureau, Alambic team, LCC Toulouse) shows that the interactions of such polyanions with the peptides tune their self-assembly, and could lessen the formation of oligomers-intermediates, that are proposed to be the most toxic form of such amyloid-forming aggregates (Figure 2).[7]

## PhD work

The PhD candidate will perform the synthesis and the characterization of the various POMs that will be studied by all the partners of the SUPRAMY project. In particular, stability studies in various buffers (pH, type of buffering agent) are a prerequisite before any study on the influence of the POMs on the aggregation.

The affinity between POM and the peptides will then be evaluated at the Institut Parisien de Chimie Moléculaire by a broad range of techniques, like isothermal calorimetry, fluorescence titration, standard NMR techniques (1D titration and DOSY experiments, including with $^{31}$P NMR), or circular dichroism (CD). Such multi-techniques approach has already proven successful for studying the interaction of POMs with various biological systems. In the case of peptide interaction with Transition Metal Substituted-POMs (TMS-POMs), a broader range of techniques (UV-Vis, EPR, luminescence, solution IR, paramagnetic NMR…) depending on the inserted ion can be used to probe the surrounding of the metal ion, thus giving additional information on the interactions and in particular the coordination site(s) to the peptide.

For the most interesting cases, advanced NMR experiments will be conducted at Laboratoire de Chimie et Biochimie Pharmacologique et Thérapeutique to probe in more details the interaction between the POM and each amyloid-forming peptide. To that end, we will combine 1D $^1$H and recent evolutions of 2D TOCSY, 2D NOESY, 2D HSQC $^1$H/$^{13}$C experiments to acquire fast and sensitive fingerprint of the prepared samples, in a time range compatible with self-assembly process.[8] We will extract structural and dynamic features of peptides and their supramolecular interactions with para-/diamagnetic TMS-POM. Notably, the paramagnetic centres will allow mapping the regions of the peptide in its vicinity. One key asset will be our ability to change the paramagnetic center in the MS-POM to finely tune its paramagnetism to the kind of NMR measurement that is sought. Some very encouraging preliminary results along this strategy have been obtained for the Aβ peptide and POMs, and will be pursued during the internship.

**Références :**


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