POLITECNICO DI MILANO

INTERNSHIP PROPOSAL

Laboratory	**Department of chemistry, materials and chemical engineering *Giulio Natta***
Research team	Laboratory of Nanostructued Fluorinated Materials (NFMLab), Via Mancinelli 7, 20131 Milan, Italy
Under the supervision of	Dr. Loic Stefan Pr. Pierangelo Metrangolo
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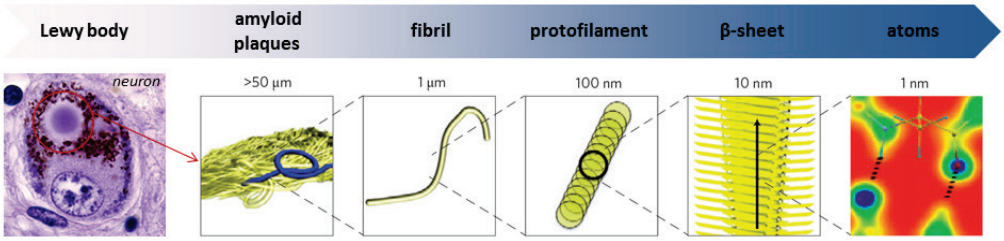
Title of the research project	**Deciphering the actual mechanism of protein self-assemblies to amyloids using halogenated peptides.**
Description	Beyond the molecular chemistry, supramolecular chemistry is a fascinating and fruitful field for researchers. This domain, mainly governed by weaker interactions (Van der Waals and electrostatic interactions, H-bonds, π-π interactions, metal complexation, etc…), is not only a lab curiosity. Indeed, Nature uses it as a pivotal and crucial process for dynamic self-assemblies: enzyme-substrate recognition, antigen-antibody association, or DNA base-pairing are only few examples illustrating the power of such supramolecular interactions.[1] In another instance, protein-protein self-assembly is of particular interest in a biological point of view, notably because of the ability of proteins to form amyloid fibrils (*figure 1*). Amyloid fibrils are insoluble structures well-known for their role in several diseases, including Alzheimer's and Parkinson's diseases, Prion's disease or type II diabetes. Interestingly, the precise mechanism of the self-assembly of proteins to amyloids is not clearly understood yet, and constitutes a major goal for chemists and biologists.[2]  ***Figure 1*** *– Hierarchy of the composition of amyloid plaques and fibrils, like in Lewy body (Parkinson's disease context).* Based on these observations, our team is focusing on the development of designed peptides and proteins able to reproduce the natural process of amyloid formation. The obtained assemblies are comprehensive models (or *modèles réduits*) helping us to decipher the role of all the constituents (type of amino-acids, hydrophobicity, global charge, etc…). Thus, this research paves the way to a global understanding of molecular and supramolecular process which are at the origin of amyloid formations in a pathological context. Based on our previous work concerning the pentapeptide Asp-Phe-Asn-Lys-Phe and its halogenated derivates (*figure 2*),[3] this internship proposal intends to focus on new series of peptides supposed to play a pivotal role in neurodegenerative diseases.

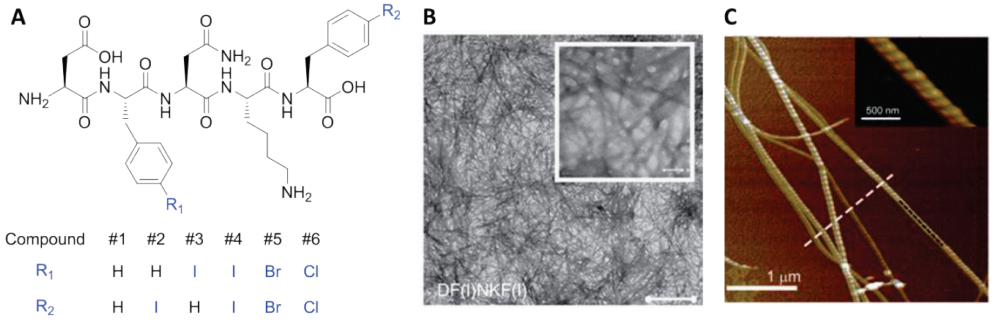


Figure 2 *– Chemical structures of the first series studied (A) and TEM (B) and AFM (C) images of compound #4, confirming the amyloid structure of the peptide self-assembly.*[3]

This work will be at the interface between chemistry, biophysics, and biology, and mainly focused on the protein-protein interactions studies.

Références:

[1] J.-M. Lehn, *La chimie supramoléculaire: concepts et perspectives*, De Boeck Université (Bruxelles, Paris), **1997**.
[2] T. P. J. Knowles, M. J. Buehler, *Nature Nanotechnol.*, **2011**, *6*, 469.
[3] A. Bertolani, L. Pirrie, L. Stefan, N. Houbenov, […] P. Metrangolo, *Nature Commun*., **2015**, *6*, 7574.

Methods used	Peptide synthesis, chemical analysis (NMR, mass) and purification (HPLC), biophysical analysis (Infrared, UV, circular dichroism, fluorescence, polarized microscopy, transmission electronic microscopy (TEM)).