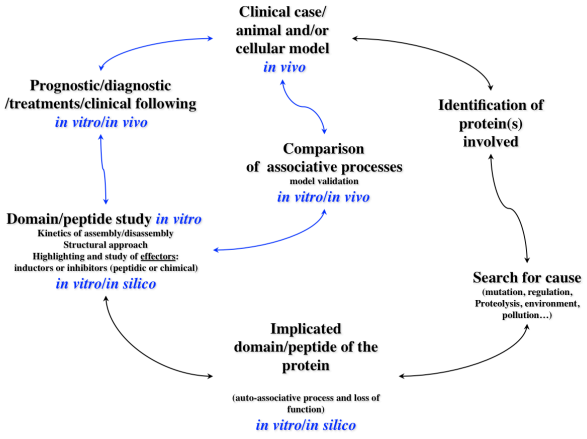
Aim 4: Pathological peptides and therapeutic peptides
(Project leader: Cyrille Garnier)

Amyloid diseases are the consequence of conformational changes in proteins that promote the formation of insoluble filamentous deposits. Accumulation of these deposits in diverse organs and tissues is involved in over thirty human diseases, notably neurodegenerative ones, such as Alzheimer's, Huntington's, Parkinson's, prion protein amyloidosis and also systemic amyloid diseases [1, 2]. These diseases are increasingly prevalent due to aging population making the study of protein amyloid aggregation processes and their regulation of major interest. Aggregates are composed of amyloid fibrils ranging in size from nano to micrometers and having common structural features characterized by a cross-beta-sheet quaternary structure. The basic component of this architecture consists in associated strands that form a long ß-sheet parallel to the fibril axis [2]. For most of the amyloid proteins, only small segments in their sequence, *i.e.* motifs of 5 to 20 amino acids long, are responsible for their aggregative properties. Therefore, synthetic peptides corresponding to these segments are commonly used as models to elucidate amyloid aggregation mechanisms. The use of short synthetic peptides has at least two advantages; first, these peptides are able to quickly self-assemble *in vitro*; and second, the amyloid-like fibrils formed *in vitro* have biophysical properties similar to their *in vivo* counterparts; making them essential tools to analyze the mechanisms of amyloid fibrillation from their morphological-functional aspects to their atomic details [3-7].

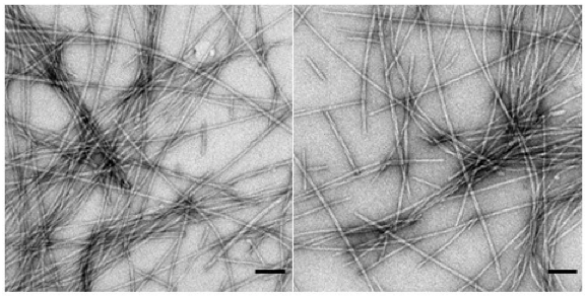
The objectives of this research project are multiple, first, is to identify and characterize the protein domain (s) involved in the auto-associative processes, second, to understand how the whole protein and/or its different domaines/segments become pathological following mutation, changes in physicochemical parameters and/or exposure to environmental pollutants. The third objective consists in a rigorous characterization of the kinetic parameters of the auto-associative processes in order to test different inhibitors. Several protein models are being studied in our team: huntingtin, tau protein, TDP-43 protein and fibrinogen. These proteins or derived peptides are responsible for various localized or systemic amyloid pathologies as they are found to aggregate in organism. This is the case in lateral amyotrophic sclerosis, frontotemporal degeneration and in many other neurodegenerative pathologies, including Alzheimer's, Parkinson's and Huntington's disease.

Our research is carried out using multiple *in silico*, *in vitro* and *in vivo* approaches. The *in silico* part allows the identification of “pathological” peptide domains by prediction of their amyloidogenicity. The *in vitro* biochemical / biophysical approach focuses on the study of the self-aggregative capacities of different mutant pathological proteins and/or different domains/peptides. Then identified domain(s) and pathological forms of the protein characterized, we focus on the understanding of the auto-associative process and its regulation by inducers (peptides, physicochemical parameters, environmental pollutants) or inhibitors (peptides or derivative, chemical molécules. The *in vivo* part consists of a stable expression of the amyloid mutant proteins in animal models on which different growth conditions (feeding or other) are applied and to which various "drugs" inhibitors showing an *in vitro* activity on amyloid aggregates such as peptides/peptide derivatives or chemical molecules.

The follow-up of the various phenotypes will allow, on the one hand, to correlate the pathogenic character of the considered mutant with the degeneration observed and, on the other hand, to discover new drugs for treatment of neurodegenerative diseases.



Identification, caracterisation, inhibition et traitment.
From involved peptide to organism.



Typical electron micrographs of amyloid fibrils formed in vitro from amyloid peptides. Scale bar 100 nm.

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