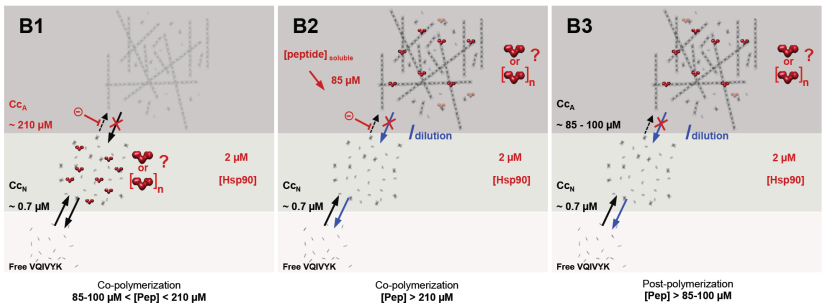
Aim 5: Chaperone proteins in neurodegenerative diseases
(Project leader: Cyrille Garnier)

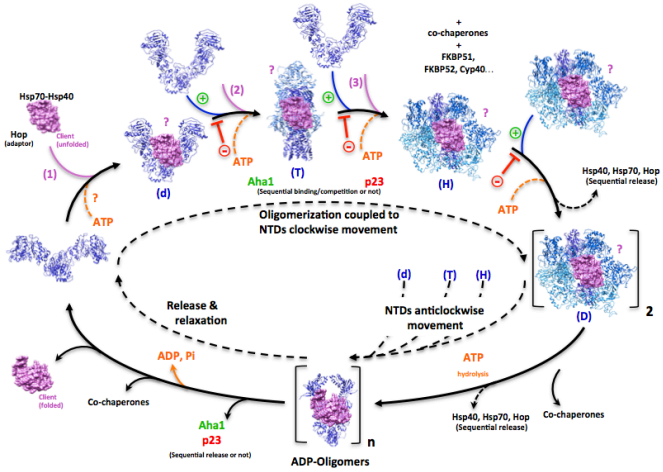
The main purpose of this research work and understand the structure/function relationship of chaperone proteins as target proteins through their regulatory roles in the structure, assembly/disassembly of cellular amyloïde target proteins. We focus on the Hsp90 chaperoning cycle and its interaction with its regulatory partners and co-chaperones. Our recent work allowed us to demonstrate that Hsp90 was involved in the regulation, in vitro, of self-assembly of amyloid peptides and proteins *[1]*. The protective effect of Hsp90 in amyloid pathologies is closely related to its oligomerization state and makes che chaperone a prime target for the development of new treatments.

Chaperone proteins play essential functions such as folding, targeting, transport, and degradation processes of most cellular proteins [2]. Among chaperones, Hsp90 is the most abundant cytosolic one, accounting for 1-2% of the total protein content in unstressed cells. Hsp90 is a homodimer wherein each monomer contains three distinct domains: (i) the ATP binding N-terminal domain (NTD); (ii) the middle domain (MD) involved in the ATP γ-phosphate hydrolysis and the client protein binding; and (iii) the C-terminal domain (CTD) involved in the dimerization process. The binding of client proteins, nucleotides and co-chaperones to Hsp90 dimer allows conformational changes crucial for its chaperoning cycle [3]. Hsp90 dimer undergoes large conformational changes induced by heat shock or divalent cations leading to its oligomerization [4, 5]. These oligomers display a typical shape similar to the “cozy nest” in which client proteins could be folded. Many studies highlight the strong involvement of molecular chaperones in the regulation of amyloid aggregation processes. For a while, Hsp90 and its co-chaperones are considered as potential new targets to treat amyloid diseases [6].

The interaction between chaperone proteins and amyloid fibrillation processes must be carefully studied due to possible contradictory experimental interpretations. Indeed, chaperone effects observed do not only depend on the studied model but also depend on the characteristics of each amyloid peptide/protein capacity to polymerize, which is driven by critical concentrations. Thus, depending on amyloid peptide/protein relative concentration compared to critical concentration, results obtained can be interpreted in contradictory ways. It is well known that for most amyloid proteins, toxic agents are small soluble oligomers rather than mature fibrils [7]. Hsp90 would sequester soluble oligomers preventing amyloid formation/propagation perhaps promoting their degradation by the proteasome. Hsp90 is involved in amyloid inhibition and Hsp90 inhibitors have proven their efficiency in the treatment of neurodegenerative diseases. Several hypotheses have been proposed to explain why Hsp90 inhibitors are efficient in amyloid diseases. Some hypotheses suggest a direct role of inhibitors towards Hsp90 whereas others suggest an indirect role. One hypothesis proposes that Hsp90 inhibitors would block the dimerization of the Hsp90 N-terminal domains preventing the release of client amyloid proteins from Hsp90 and therefore leading to their degradation. Thus, Hsp90 inhibition would drive amyloid protein clearance through their orientation to proteasome [6]. In other words, inhibitors would increase the sequestering effect of Hsp90. On the other hand, when the system is overbooked, Hsp90 would bind and stabilize fibrils preventing their dissociation.



Interaction of Hsp90 with VQIVYK peptide amyloid structures and modulation of fibrils assembly/disassembly [1].



***Model for the Hsp90 chaperone cycle involving Hsp90 oligomers** [Lepvrier, E.; Thomas, D. and Garnier C., Hsp90 quaternary structures and the chaperone cycle: highly flexible dimeric and oligomeric structures and their regulation by co-chaperones, **2017** in press]*

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