Contribution ID: **20** Type: **not specified**

# Understanding the interaction between Aβ42 and β-amyloid aggregation inhibitors: a mass spectrometry based-approach

*Wednesday, 21 June 2023 16:40 (15 minutes)*

Neurodegenerative disorders (NDs) such as Alzheimer's disease (AD), Parkinson's disease (PD) and prion diseases are some of the most common forms of age-related diseases. Even if pathogenesis of these neurodegenerative diseases remains unclear, increasing evidence point out a common critical molecular process involving the assembly of various aggregated proteins with a β-sheet conformation, referred to as amyloids.[1] The inhibition of this process could be a viable therapeutic strategy for the treatment of neurodegenerative diseases. Peptide based inhibitors of β-amyloid fibrillation can prevent Aβ aggregation into fibrils by binding the protein and are emerging as safe drug candidates as well as interesting compounds for early diagnosis of AD.[2] The identification of adducts formation by means of mass spectrometry techniques, can be used to obtain a direct evidence of the interaction between Aβ42 and its aggregation inhibitors. These interactions can alter peptide-chain flexibility affecting the cleavage of the peptide bonds by a protease. Moreover, interactions can also occur at the peptide bonds involved in the proteolytic cleavage in turn affecting enzyme's accessibility to the cleavage sites. Therefore, the identification of proteolysis resistant peptides fragments, by mass spectrometry, may reveal the amino acid residues involved in the interaction of Aβ42 with specific molecules. Here we report studies using mass spectrometry techniques to investigate the interaction of Aβ42 monomer with conjugated peptides that we recently proposed as aggregation inhibitors.[3-5] All the results observed indicate a different behaviour of the proposed molecules on the proteolytic pattern of Aβ. Compelling evidences were observed when interactions concerned the N-terminal domain of the protein. Understanding the effect of these interactions on the aggregation processes, at the molecular level, will enable to outline the features of new and more effective aggregation inhibitors.

References

[1] C. A. Ross, M. A. Poirier, Nat. Med. (2004), 10, S10

[2] A. J. Doig and P. Derreumaux, Curr. Opin. Struct. Biol. (2015) 30, 50.

[3] G.M.L. Consoli, R. Tosto, A. Baglieri, S. Petralia, T. Campagna, G. Di Natale, S. Zimbone, M.L. Giuffrida, G. Pappalardo, ACS Chem. Neurosci., (2021), 12, 1449.

[4] Zimbone, S.; Giuffrida, M. L.; Sabatino, G.; Di Natale, G.; Tosto, R.; Consoli, G. M. L.; Milardi, D.; Pappalardo, G.; Sciacca, M. F. M. ACS Chem. Neurosci. 2023, 14 (6), 1126.

[5] V. Villari, R. Tosto, G. Di Natale, A. Sinopoli, M.F. Tomasello, S. Lazzaro, N. Micali, G. Pappalardo, ChemistrySelect., (2017), 2, 9122.

**Presenter:** Dr DI NATALE, Giuseppe (IC-CNR)

**Session Classification:** Session