University of Naples Federico II
Department of Pharmacy
Doctoral Course in Pharmaceutical Sciences XL Cycle

METALLODRUGS AS MODULATORS OF AMYLOID B AGGREGATION IN NEURODEGENERATIVE DISEASES

Tutor Daniela Marasco and Co-tutor Lucia Falcigno

Metallodrugs have a wide clinically accepted range of applications in cancer and inflammatory diseases and more recently they have been proposed as novel and selective neurodrugs [1] Neurodegenerative diseases (NDDs) imply amyloid aggregation of proteins leading to fibrillar states and plaques formation. Unraveling how modulators interact with amyloids and change their aggregation process may provide opportunities for the development of therapies [2] since the modulation of fibrillar growth may regulate the final size and shape of non-covalent assemblies [3]. In detail transition metal complexes exhibit unique features due to different oxidation and spin states of central ions and coordination geometries and ligand fields tuned through substitution of ligands, oxidation and hydrolysis of substrates. Metallodrugs demonstrate able to interfere with amyloid aggregation: Pt, Pd, Au and Ru compounds modulate early stages of amyloid aggregation [4] [5]. In this project, the ability of metal complexes to modulate the aggregation of amyloid systems will be investigated to achieve selectivity toward different amyloid systems [6] [4] [7]. The design, chemical synthesis and in vitro functional and structural characterization will be carried out by means of different spectroscopic (e.g., fluorescence, UV-vis, and electrospray ionization mass spectrometry) and microscopic (scanning electron microscopy) techniques. Design and characterization of metal complexes as well as of amyloid polypeptides will be followed by biochemical in vitro binding assays and SAR investigations, also through NMR studies. Further subsequent optimization will be carried out in cellular NDDs lines (as SHSY5) to evaluate their effects and detail their Mechanisms Of Action (MOAs).

[1] H.Y. Khan, A. Ahmad, M.N. Hassan, Y.H. Khan, F. Arjmand, R.H. Khan, Advances of metallodrug-amyloid β aggregation inhibitors for therapeutic intervention in neurodegenerative diseases: Evaluation of their mechanistic insights and neurotoxicity, Coordination Chemistry Reviews 501 (2024) 215580.
[2] K.L. Stewart, S.E. Radford, Amyloid plaques beyond Aβ: a survey of the diverse modulators of amyloid aggregation, Biophysical reviews 9(4) (2017) 405-419.
[3] L. Zhu, Y. Song, P.-N. Cheng, J.S. Moore, Molecular design for dual modulation effect of amyloid protein aggregation, Journal of the American Chemical Society 137(25) (2015) 8062-8068.
[4] S. La Manna, M. Leone, I. Iacobucci, A. Annuziata, C. Di Natale, E. Lagreca, A.M. Malfitano, F. Ruffo, A. Merlino, M. Monti, Glucosyl platinum (II) complexes inhibit aggregation of the C-terminal region of the Aβ peptide, Inorganic Chemistry 61(8) (2022) 3540-3552.
[5] D. Florio, A.M. Malfitano, S. Di Somma, C. Mugge, W. Weigand, G. Ferraro, I. Iacobucci, M. Monti, G. Morelli, A. Merlino, D. Marasco, Platinum(II) O,S Complexes Inhibit the Aggregation of Amyloid Model Systems, Int J Mol Sci 20(4) (2019).
[6] S. La Manna, V. Roviello, F. Napolitano, A.M. Malfitano, V. Monaco, A. Merlino, M. Monti, K. Kowalski, Ł. Szczupak, D. Marasco, Metal-Complexes Bearing Releasable CO Differently Modulate Amyloid Aggregation, Inorganic Chemistry (2023).
[7] S. La Manna, C. Di Natale, V. Panzetta, M. Leone, F.A. Mercurio, I. Cipollone, M. Monti, P.A. Netti, G. Ferraro, A. Terán, A Diruthenium Metallodrug as a Potent Inhibitor of Amyloid-β Aggregation: Synergism of Mechanisms of Action, Inorganic Chemistry 63(1) (2023) 564-575.

The described project is part of the following project:
“National Recovery and Resilience Plan (NRRP), project MNESYS (PE0000006) – A Multiscale integrated approach to the study of the nervous system in health and disease (DN. 1553 11.10.2022)