Developing chimeric small molecules for neurodegeneration: a medicinal chemist' s perspective

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Chimeric molecules, i.e., engineered constructs in which two or more functional components are linked, are not a novelty in medicinal chemistry. A pioneering contribution to the field was provided by P.S. Portoghese, with the development of 'bivalent' ligands for opioid receptors. In the last two decades, the strategy has been recognized as an effective approach to design ligands able to modulate multiple targets in a polypharmacology context. Chimeric compounds can be obtained by linking (presence of a linker) or framework integration (merging or fusing) strategies. Although very promising to combat the multifactorial nature of complex neurodegenerative diseases, their development faces the critical issues of selecting the right target combination and the achievement of a balanced activity towards them, while maintaining drug-like-properties. Importantly, several neurodegenerative diseases have been successfully tackled using chimeric molecules, and expansion of knowledge in this area by including the emerging proteolysis targeting chimeras (PROTACs),[1] might be a key opportunity for traversing the "Valley of Death". Here, I will highlight lessons learned about chimeric molecules against Alzheimer's disease[2] and amyotrophic lateral sclerosis,[3] which could expand the toolbox for neurodegenerative drug discovery.

References:

1. Salerno, A.; Seghetti, F.; Caciolla, J.; Uliassi, E.; Testi, E.; Guardigni, M.; Roberti, M.; Milelli, A.; Bolognesi, M. L. Enriching Proteolysis Targeting Chimeras with a Second Modality: When Two Are Better Than One. *J Med Chem* **2022**, *65*, 9507-9530.
2. Gandini, A.; Gonçalves, A.E.; Strocchi, S.; Albertini, C.; Janočkov, A.; Tramarin, A.; Grifoni, D.; Poeta, E.; Soukup, O.: Muñoz-Torrero, D.; Monti, B.; Sabaté, R.; Bartolini, M.; Legname, G.; Bolognesi, M. L. Discovery of dual Aβ/Tau inhibitors and evaluation of their therapeutic effect on a Drosophila model of Alzheimer's diseases. *ACS Chem Neurosci* **2022**, *13,* 23, 3314–3329.
3. Albertini, C.; Salerno, A.; Atzeni, S.; Uliassi, E.; Massenzio, F.; Maruca, A.; Rocca, R.; Mecava, M.; Silva, F. S. G.; Mena, D.; et al. *ACS Chem Neurosci* **2022**, *13*, 15, 2252-2260.