Multi-target kinase inhibitors for effective control of neuroinflammation

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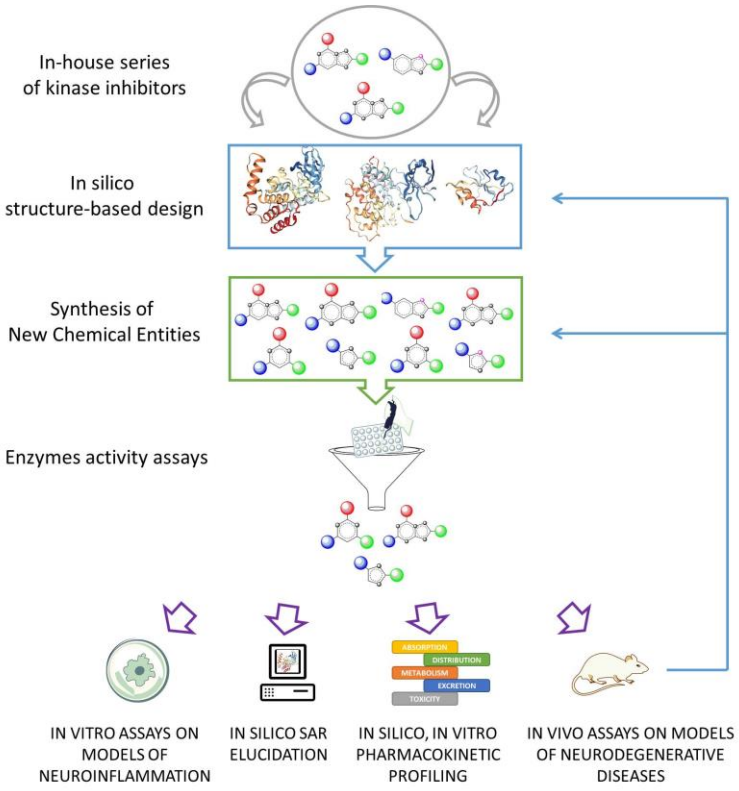
Evidence exists that neuroinflammation plays a crucial role in the development and progression of many chronic neurological diseases: Alzheimer's disease (AD), Multiple Sclerosis (MS), Amyotrophic Lateral Sclerosis (ALS) and Parkinson's disease (PD). Despite years of research, drug discovery initiatives, and promising clinical trials, these diseases remain incurable.[1] Both microglial cells and astrocytes act as important regulators of CNS inflammation.[2] The present project aims to use a chemical biology approach to shed light on the role of GSK-3β, CK-1δ and FYN protein kinases on the microglia/astrocytes-mediated neuroinflammatory process, aiding in the translation in new approaches to counteract these debilitating chronic neurological diseases.



Starting from work previously done in our group,[3] the main goal of this project is to carry out an intensive campaign of chemical synthesis to obtain potent and selective chemical probes against the above-reported molecular targets. However, design and synthesis of a focused library of multi-target ligands will help to identify potential synergistic and/or additive effects derived from the simultaneous modulation of two or more molecular targets.[4] The new chemical entities will be designed to be compliant with the physicochemical requirements for CNS delivery. All the molecules will be in vitro tested by means of biochemical assays in order to obtain an extensive structure activity relationship. Thus, the PhD student will also optimize/develop the appropriated enzyme activity assays. Therefore, with the help of collaborations, the project will develop in a clear temporal and methodological progression, from structure/ligand-based design to synthesis, to biochemical and pharmacological characterization. In particular, advanced computational approaches will be used to investigate the molecular determinants responsible for the target-ligand interaction and pharmacokinetics profiles of compounds will be determined by both in silico, in vitro and in vivo studies. Then, assays on astrocytes and microglia cultures will be performed in order to understand the roles of target on the neuroinflammatory process. Finally, selected compounds will be studied in vivo disease models. Thus, the project is characterized by a strict interconnection between the involved actors, thus the PhD student will work in a strongly interdisciplinary environment.

References:

1.Amor, S. et al. *Immunology* 2014, 142, 151.
2.Colombo, E. et al. *Trends Immunol*. 2012, 37, 608; Luo, X. G. et al. *Transl. Neurodeg*. 2012, 1, 9.
3.Bissaro, M. et al. *ChemMedChem* 2018, 13, 2601; Federico, S. et al. *ChemMedChem* 2019, 14, 310.
4.Garuti, L. et al. *Curr. Med. Chem*. 2015, 22, 695.