Topic: Identification of new bioactive molecules by computational methods

Tutor: Prof. Caterina Fattorusso (SSD CHIM/08) **- Co-tutor:** Prof. Marco Persico (SSD CHIM/08)

The relationship between shape and function is one of the key concepts on which the organization of biological systems is based, similarly, the relationship between a drug structure and its biological activity is a basic concept in medicinal chemistry. It is known that proteins control complex allosteric networks responding to changes in the cellular environment by switching between different conformational states, and an increasing amount of evidences support the hypothesis that nucleic acids share similar properties. Indeed, a change in the shape corresponds to a change in the function through the binding to alternative biomolecular partners. These can be small endogenous ligands as well as biopolymers, such as, other proteins and/or nucleic acids. In any case, it has been demonstrated that the binding affinity is due to the interaction with specific sub-structures called "hot spots"[1] often present in just one of the possible conformational states of the interacting biomolecules.

On this background, the present project aims at the identification/design of molecules able to reproduce the "structural code" of biological systems and to recognize and bind the desired target(s) according to its(their) conformation/function. On the basis of our previous achievements in the field[2-9] and our ongoing collaborations, the main molecular targets under investigation will be: proteasome, prion protein, and the motifs/domains responsible for coronaviruses invasion and diffusion, such as the heptad repeat motif present in the Spike protein,[10] together with the protein domain responsible for the interaction between Sars-Cov2 non structural protein nsp10 and its partners nsp14 and nsp16.[11] Moreover, the structure-function relationships of analogues of miRNA able to restore sensitivity to paclitaxel in resistant tumor cells through the down-regulation of STAT3 e RAP1A,[12] will be also investigated. A first phase of the project will be devoted to the identification of the proper hot spots for the binding of molecular partners able to modify the desired target function. This will be followed by the building of molecular and/or pharmacophore models that will allow to drive the rational identification/design of new molecular hits able to interact with such hot spots, as well as to optimize structure/activity of bioactive compounds. The research will be carried out by using all software and facilities present at the Laboratory of Excellence of Molecular Modelling (LMM; https://www.farmacia.unina.it/laboratori-di-eccellenza/lmm).

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