Offre de stage Master 2

Title: Synthesis of chemical inhibitors of ubiquitin-binding protein p62 (sequestosome-1 protein) and new PROTACs (Proteolysis Targeting Chimera) to circumvent Bortezomid resistance in Multiple Myeloma and Mantel Cell Lymphoma.

Collaboration with Manuel S. Rodriguez, ITAV, UBICARE research team

State of the art: Protein homeostasis is critical to regulate all cellular functions. The Ubiquitin-Proteasome and Autophagy-Lysosome systems are crucial to maintain protein equilibrium. Recent findings indicate that these two proteolytic systems communicate with each other under physiologic or pathologic conditions. The use of conventional autophagy inhibitors revealed a process were the proteasome is degraded by autophagy, a process that was named proteaphagy. Proteaphagy is clinically relevant since it is found in patients with resistance to chemotherapy. This selective autophagy event involves the participation of the p62/Sequestosome-1 protein that recruits the proteasome into autophagosome for its degradation. Tackling p62 and ubiquitin enzymes regulating proteaphagy with new chemical inhibitors will provide a better understanding of this proteolytic crosstalk. Furthermore, this strategy will also generate important information on the apoptotic factors implicated in the cell killing response in chemo-resistant cells and improve the actual therapies where proteostasis is disrupted.

Objectives: The first objective of this project is to synthesize new chemical inhibitors of p62 to tackle proteaphagy. The activity of these new inhibitors will be compared in vitro to the activity of a well-established p62 inhibitor acting on its ZZ domain named XRK3F2. The second objective is to manipulate the activity of ubiquitin enzymes using proteolysis targeting chimeras (PROTACs) targeting TRIM24. New synthetic pathways will be explored to generate new PROTACs able to tackle these crucial cellular factors. Finally, preliminary efficacy studies are planned to be performed first in distinct cellular MCL and MM models of acquired and innate resistant to the proteasome inhibitor Bortezomib.

Facilities: chemistry will be performed at the LCC in the "dendrimer and heterochemistry" group under the supervision of Cédric-Olivier Turrin, and the biochemical studies will be performed under the supervision of Manuel Rodriguez in the UBICARE research group located at the ITAV.

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