Internship proposition
One page max
M2 I3/0HNU 2024-25

Lab: CRCI2NA Inserm U1307 CNRS 6075

team: Team 9 - CHILD

Name and position of the supervisor: LAMOUREUX Francois, CR INSERM

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Candidate: PITHON Antoine

Title of the internship: **Autophagy inhibition using lysosomotropic agents sensitizes osteosarcoma cells to the novel GCN2 kinase activator NXP800**

Summary of the internship proposal:
Osteosarcoma (OS) is an aggressive primary bone tumor affecting young people, and is often associated with resistance to conventional therapies, thus necessitating the development of new therapeutic strategies. A tumor cell is exposed to high levels of stress due to nutrient and oxygen deprivation, genetic mutations and exposure to chemotherapies, making cellular stress a vulnerability to target. We recently demonstrated the preclinical efficacy of a small molecule GCN2 kinase activator, NXP800, that induces Endoplasmic Reticulum (ER) stress and prolonged Unfolded Protein Response (UPR) leading to cell death in OS cells. Despite impressive efficacy in some tumor cells, clinical responses to NXP800 could be limited by the emergence of resistance mechanisms as frequently observed with various small molecules inhibitors. We investigated the prosurvival pathways activated in response to NXP800, and identified an activation of autophagy. Indeed, the role of autophagy in cancer can be dual, inducing tumor cell death or protecting tumor cells from unfavorable conditions, thus acting as an anti-apoptotic mechanism maintaining metabolism and energy needed for survival. Taken together, these data suggest that autophagy is a good candidate to target in order to sensitize OS cells to NXP800 treatment.
This study will investigate the synergistic potential of combining lysosomotropic agents with NXP800 to enhance the susceptibility of osteosarcoma cells to treatment. Lysosomotropic agents, known for their ability to disrupt lysosomal function and inhibit autophagy, are hypothesized to sensitize cancer cells by impairing their survival mechanisms. Through a series of in vitro and in vivo experiments, we will demonstrate that the combination therapy will exhibit a potent cytotoxic effect compared to either agent alone, providing a proof of concept of a potential combinatorial approach for overcoming OS resistance and improving clinical outcomes.
Option(s) linked to the project:

☐ Clinical Research Profile
☐ Data Analyst Profile
☒ Experimental Biology Profile