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

Lab: CRCI2NA

Team: Molecular Vulnerabilities of Tumor Escape in B-cell malignancies, team 11

Name and position of the supervisor: Catherine Pellat, DR CNRS & Patricia Gomez, CH CHU

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Candidate:

Title of the internship: **Role of p53/BAX and VDAC2/BAK interactions in the mitochondrial resistance to death**

Summary of the internship proposal: In B-cell malignancies, mitochondria are resistant to apoptosis through overexpression of one or several anti-apoptotic proteins of the BCL2 family, MCL1, BCL2, BCLxL. These proteins sequester pro-apoptotic (BIM, NOXA, etc.) and effector (BAK, BAX) proteins of the BCL2 family, preventing them from inducing mitochondrial depolarization and subsequent cell death. However, this resistance related to the overexpression of these complexes is a therapeutic vulnerability to BH3 mimetics, molecules which have been developed to precisely target anti-apoptotic proteins and compete with pro-apoptotic and effector proteins. This latent potential for mitochondrial depolarization is known as "priming for death". Our recent and ongoing work in isogenic cells expressing or not p53 or VDAC2 shows that both p53 (Durand R, Blood 2024) and VDAC2 (Champion, in preparation) control the mitochondrial priming: the response to BH3 mimetics is controlled by BAX expression that is transcriptionally regulated by p53 in p53-competent cells, and by BAK expression that is directly controlled by VDAC2 in p53-deficient cells. Beyond its activity as a transcription factor in the nucleus, p53 interacts directly with BCL2 family proteins at the mitochondria to promote apoptosis. The aim of this internship is to study the nature and complexes of apoptosis effectors BAX and BAK with BCL2 family members, p53 and VDAC2, in isogenic cells expressing or not wild-type or mutant p53, and to determine the impact of VDAC2 inhibition on these complexes. The candidate will study the cellular response to the combination of BH3 mimetics with VDAC2 modulation, as well as the regulation of protein-protein interactions at the mitochondria in the different p53 backgrounds. The candidate will develop skills in cellular biology, biochemistry and gene editing.

Option(s) linked to the project:
☐ Clinical Research Profile
☐ Data Analyst Profile
☒ Experimental Biology Profile