Internship proposition
One page max
M2 0HNU 2025-26

Lab: CRCI2NA
Team: REMOVE-B (Team 11)
Name and position of the supervisor: Patricia Gomez-Bougie, CR CHU Nantes. Catherine Pellat-Deceunynck DR CNRS.
Email of the supervisor: patricia.gomez@inserm.fr; catherine.pellat-deceunynck@univ-nantes.fr
Candidate: Solène Sepré
Title of the internship: "Reprogramming the apoptotic machinery of multiple myeloma cells via activation of the STING-IRF3 pathway to counteract TP53 abnormalities"
Summary of the internship proposal:

Multiple myeloma (MM) is a B-cell malignancy in which deletion and/or mutations of *TP53* are associated with treatment resistance and reduced patient survival. Identifying alternative therapies capable of overcoming *TP53*-related resistance is a major challenge in cancer research.
This project aims to bypass the therapeutic barrier imposed by *TP53* abnormalities through direct activation of the cGAS/STING pathway. Beyond its role in activating innate immunity, this pathway might play a broader role in regulating cell death, notably through the control of expression and function of pro-apoptotic proteins, particularly those belonging to the BCL2 family. Our preliminary results show that activation of STING by a clinically investigated agonist, diABZI, in combination with the BH3 mimetic targeting MCL1 (S63845), induces a significant increase in apoptosis, especially in *TP53*-deficient cells (*TP53-/-*), and even more pronouncedly in *TP53*-mutated cells (*TP53R175H*).
Understanding the mechanisms underlying this response, particularly the interplay between the STING/IRF3 and the apoptotic pathway, mainly through transcriptional and functional regulation of BCL2 family members, could help to evaluate the potential of the STING/IRF3 pathway as a therapeutic target in MM. This potential could be harnessed through STING agonists, which are currently undergoing clinical evaluation.

Publications related to the subject (last 5 years):

- Champion O, Maïga S, Antier C, Dousset C, Moreau-Aubry A, Bellanger C, Guillonneau F, Descamps G, Moreno JA, Kwon O, Lilli NL, Moreau P, Chiron D, **Pellat-Deceunynck C**, Touzeau C, **Gomez-Bougie P.** VDAC2 primes Myeloma cells for BAK-dependent apoptosis and represents a novel therapeutic target. Leukemia. 2025 Apr;39(4):995-1000
- Durand R, Bellanger C, Descamps G, Dousset C, Maïga S, Derrien J, Thirouard L, Bouard L, Asnagli H, Beer P, Parker A, **Gomez-Bougie P**, Devilder MC, Moreau P, Touzeau C, Moreau-Aubry A, Chiron D, **Pellat-Deceunynck C**. Combined inhibition of CTPS1 and ATR is a metabolic vulnerability in p53-deficient myeloma cells. Hemasphere. 2024 Oct 8;8(10):e70016.
- Durand R, Descamps G, Bellanger C, Dousset C, Maïga S, Alberge JB, Derrien J, Cruard J, Minvielle S, Lilli NL, Godon C, Le Bris Y, Tessoulin B, Amiot M, **Gomez-Bougie P**, Touzeau C, Moreau P, Chiron D, Moreau-Aubry A, **Pellat-Deceunynck C**. A p53 score derived from TP53 CRISPR/Cas9 HMCLs predicts survival and reveals a major role of BAX in the response to BH3 mimetics. Blood. 2024 Mar 28;143(13):1242-1258
- Seiller C, Maiga S, Touzeau C, Bellanger C, Kervoëlen C, Descamps G, Maillet L, Moreau P, **Pellat-Deceunynck C**, **Gomez-Bougie P**, Amiot M**.** Dual targeting of BCL2 and MCL1 rescues myeloma cells resistant to BCL2 and MCL1 inhibitors associated with the formation of BAX/BAK hetero-complexes. Cell Death&Dis, 2020 May 5;11(5):316.

Option(s) linked to the project:
☒ Hematology
☐ Immunology-Cancerology
☐ Oncology
☐ Nuclear Medicine

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