Master Biologie Moléculaire et Cellulaire
Université de Paris - *UFR Sciences du Vivant*

Parcours : **Biologie et Développement Cellulaires 'BDC'**
http://www.master2bdc.fr/
Fiche de Projet de Stage M2. Année 2026-2027

Unité : UMR9019 CNRS – Gustave Roussy **Intitulé Equipe :** *Genotoxic stress, Checkpoint response and Cancers* team **ED d'appartenance :** ED Cancérologie CBMS 582 **Responsable de l'Equipe :** Olivier Gavet	**Responsable du Stage : Olivier Gavet** Dr Olivier GAVET GUSTAVE ROUSSY UMR9019 CNRS Pavillon de recherche 2 114, rue Edouard Vaillant 94805 - VILLEJUIF cedex Tel office: +33 1 42 11 56 83 https://umr9019.com/team-6/

Titre du projet :

Exploring the functional limitations of DNA surveillance checkpoints to prevent the appearance of a genetic instability during tumorigenesis

Résumé du Projet :
Maintaining genome integrity is essential for cell survival and tissue homeostasis. Every day, cells experience thousands of DNA lesions generated as a consequence of metabolic activity and its by-products. To cope with these insults, cells activate the DNA Damage Response (DDR), a signaling network that coordinates DNA repair with **surveillance checkpoints to prevent the transmission of damaged DNA to daughter cells.**
Two major checkpoint pathways, ATR/Chk1 and ATM/Chk2, are activated in response to replication stress and DNA double-strand breaks, respectively. These pathways delay cell-cycle progression and prevent mitotic entry until DNA lesions have been resolved. Yet, accumulating evidence indicates that cells can enter mitosis despite persistent DNA damage or incomplete DNA replication, thereby promoting chromosome instability.
The molecular mechanisms allowing cells to bypass active checkpoint signaling remain poorly understood. Identifying these mechanisms is particularly important in the context of tumorigenesis, as replication stress is a hallmark of precancerous lesions induced by oncogene activation, such as Myc, Cyclin E. Functional limitations of checkpoint signaling under these conditions may significantly **contribute to tumorigenesis and aggressiveness** through the accumulation of genetic alterations.

In this Master 2 project, the candidate will investigate the contribution of several candidate proteins in:
- ATR/Chk1 checkpoint override under replication stress;
- ATM/Chk2 checkpoint override following DNA double-strand break induction;
- The generation of genome instability resulting from premature mitotic entry.
Experimentally, the work will involve time-lapse live-cell imaging of genetically engineered fluorescent cell lines subjected to the depletion or pharmacological inhibition of candidate proteins. A substantial part of the project will consist of image analysis and quantification to determine the contribution of these proteins to checkpoint override.

Publications de l'équipe relatives au stage:

. Lebrec V. and **Gavet O.** (**2024**). *Monitoring Chk1 kinase activity dynamics in live single cell imaging assays.* ***Chapter book in Methods in Cell Biology***,
. Lebrec V., Poteau M., Morretton J.P. and **Gavet O.** (**2022**). *Chk1 dynamics in G2 phase upon replication stress predict daughter cell outcome.* **Developmental Cell** Mar 14;57(5):638-653. **IF: 13.4**
. N Tavernier, Y Thomas, S Vigneron,..., G Gasmi-Seabrook, N Joly, M Poteau, G Velez-Aguilera, **O Gavet**, A Castro, M Dasso, T Lorca, F Sicheri, and L Pintard (2021) *Bora phosphorylation substitutes in trans for T-loop phosphorylation in Aurora A to promote mitotic entry*. **Nature Communications** Mar 26;12(1):1899. **IF: 16.6**