Master Biologie Moléculaire et Cellulaire 'BMC',
Université Paris Cité - *UFR Sciences du Vivant*

Parcours : **Biologie et Développement Cellulaires 'BDC'**
https://master2bdc.ijm.fr/
Fiche de Projet de Stage de M2, 2025-2026

Unité INSERM ou CNRS ou Université : Centre de Recherche des Cordeliers U1138 **Intitulé Equipe : Instabilité génomique, métabolisme, immunité et tumorigenèse hépatique** **ED d'appartenance : ED 562 BioSpc** **Responsable de l'Equipe : Dr Chantal DESDOUETS**	**Responsable du Stage : Dr Chantal DESDOUETS / Dr Séverine CELTON-MORIZUR** **Contacts** Adresse : 15 rue de l'école de médecine Email : chantal.desdouets@inserm.fr / severine.morizur@inserm.fr Tel : 01 44 27 24 77

Titre du projet : The cGAS-STING-Genomic Instability Crosstalk in Liver Cancer

Résumé du Projet de Stage (en 300 mots maximum, mots clés en gras)

This M2 project offers a compelling investigation into the complex **role of the cGAS-STING pathway in Hepatocellular Carcinoma (HCC)**, a globally impactful liver cancer with rising incidence and limited therapeutic options. This research is particularly pertinent given the dual nature of cGAS-STING signaling, which can be both anti-tumoral and paradoxically immune-suppressive when chronically activated. HCC presents a significant global health challenge, characterized by high mortality and a lack of effective treatments. It is broadly categorized into two main groups: (1) Cluster A (proliferation), an aggressive form marked by chromosomal instability and frequent TP53 mutations. (2) Cluster B (non-proliferation), less aggressive, associated with CTNNB1 mutations and chromosomal stability. While the cGAS-STING pathway is recognized for its role in initiating anti-tumor immunity, its precise function in HCC, especially concerning varying degrees of genomic instability, remains undefined. This project will address this critical gap by investigating how genomic instability and the cGAS-STING pathway interact to influence HCC development.

The central hypothesis is that the cGAS-STING pathway's role in HCC is highly context-dependent, particularly in the presence of genomic instability. Our research aims to:

- Determine whether cGAS-STING signaling promotes or suppresses tumor development in different HCC contexts.
- Elucidate the impact of cGAS-STING signaling on immune surveillance of DNA-damaged hepatocytes and the overall hepatic immune response during disease progression.
- Identify potential prognostic and therapeutic targets by correlating STING expression and DNA lesion accumulation with human HCC development.

The experimental approach will primarily utilize relevant mouse models that mimic both chromosomally stable (beta-catenin gain-of-function) and chromosomally unstable (p53 loss-of-function) forms of HCC. These models will include mice with mutations in STING and cGAS, allowing for a detailed investigation of their individual and combined effects. The M2 student undertaking this project will benefit from a highly collaborative research environment and gain proficiency in a range of cutting-edge technological approaches (Digital pathology, Multispectral imaging, RNA-Seq analyses, Flow cytometry)

Ultimately, this project seeks to unravel the intricate mechanisms by which genomic instability influences HCC progression via the cGAS-STING pathway. The insights gained from this research are expected to pave the way for the identification of novel therapeutic strategies, offering new hope for patients battling this devastating disease.

Publications de l'équipe relatives au projet de stage (max 5)

Replication stress triggered by nucleotide pool imbalance drives DNA damage and cGAS-STING pathway activation in NAFLD. Donne R, Saroul-Ainama M, Cordier P, Hammoutene A, Kabore C, Stadler M, Nemazanyy I, Galy-Fauroux I, Herrag M, Riedl T, Chansel-Da Cruz M, Caruso S, Bonnafous S, Öllinger R, Rad R, Unger K, Tran A, Couty JP, Gual P, Paradis V, Celton-Morizur S, Heikenwalder M, Revy P, Desdouets C. **Dev Cell**, 2022. doi: 10.1016/j.devcel.2022.06.003.

Structure, Dynamics, and Impact of Replication Stress-Induced Structural Variants in Hepatocellular Carcinoma. Bayard Q, Cordier P, Péneau C, Imbeaud S, Hirsch TZ, Renault V, Nault JC, Blanc JF, Calderaro J, Desdouets C, Zucman-Rossi J, Letouzé E. **Cancer Res**, 2022. doi: 10.1158/0008-5472.