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

Parcours : **Biologie et Développement Cellulaires 'BDC'**
http://www.master2bdc.fr/
Fiche de Projet de Stage de M2, 2022-2023

Unité INSERM ou CNRS ou Université : **UMR 3666 CNRS U1143 Inserm - Institut Curie**	**Responsable du Stage : Cedric BLOUIN**
Intitulé Equipe : Mécanique et Dynamique Membranaires de la Signalisation Intracellulaire	**Contacts** Adresse : Institut Curie 26 rue d'Ulm 75005 Paris
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Titre du projet: Mechanical forces and cancer: Impact on IFN gamma receptor membrane nano-partitioning and function

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

Cells feel their surrounding environment through their plasma membrane. Among the extracellular signals it integrates, **mechanical forces** appear to be particularly involved in tissue development but also in tumor progression. **Interferons** (IFNs) are pleiotropic cytokines that play key roles in innate and adaptive immunity for host defense against intracellular infections and **tumor control**. IFN binding to the IFN receptors trigger the downstream activation of the **JAK/STAT signaling** pathway whose dysregulation has been involved in the pathogenesis of autoimmune and inflammatory diseases, and cancer. Our multidisciplinary research project aims at investigating the poorly explored effects of mechanical forces on nanopartitioning at the plasma membrane (PM) of the **IFN gamma receptor** (IFN-γR). It relies on recent discoveries and developments from our laboratory:

1) the demonstration of the fundamental role of the IFN-γR dynamic partitioning with specific PM **lipid nanodomains** in JAK/STAT signaling pathway activation (*Cell* 2016),
2) the engineering of micrometer scale technologies to apply **mechanical constraints** on cells in 2D or 3D environments to mimic solid tumors (*Nat Commun* 2019).

In this project, we want to test the original hypothesis that PM lipid nano-partitioning and associated signaling pathways are altered or modulated by the mechanical forces that cancer cells encounter within solid tumors such as breast cancers. Therefore, the candidate will apply different mechanical stimulations that we have designed to mimick the mechanical micro-environment of solid tumors: hypo-osmotic shock, uni-axial stretching and cell compression on several **tumor cell lines** immortalized from triple negative breast cancers (TNBC): Hs-578T, MDA-MB-231 and MDA-MB-436 showing increasing aggressiveness. In parallel, the candidate will produce uncompressed/compressed **spheroids** of these cancer cells. Using **biochemistry** and **advanced microscopy techniques**, we will monitor IFN-γR localization at the PM, the activation status of JAK/STAT signaling under IFN-γ stimulation, and whether it modifies the evolution of EMT marker levels (E- and N-cadherin, Vimentin…) and PD-L1 within the constrained microenvironment.

Publications de l'équipe relatives au projet de stage (max 5) (PhD students are underlined, *contributed equally)

- Thoidingjam LK*, **Blouin CM***, …, Lamaze C, Rodriguez R. Small Molecule Inhibitors of Interferon-Induced JAK-STAT Signalling. *Angew Chem* (2022) doi: 10.1002/anie.202205231
- Morana O, …, **Blouin CM**, Lamaze C, Lorizate M, Contreras FX. Identification of a New Cholesterol-Binding Site within the IFN-γ Receptor that is Required for Signal Transduction. *Adv Sci* (2022) 9(11):e2105170
- Dewulf M, …, Lamaze C*, **Blouin CM***. Dystrophy-associated caveolin-3 mutations reveal that caveolae couple IL6/STAT3 signaling with mechanosensing in human muscle cells. *Nat Commun* (2019) 10(1):1974
- **Blouin CM***, Hamon Y*, Gonnord P*, …, He HT, Lamaze C. Glycosylation-Dependent IFN-γR Partitioning in Lipid and Actin Nanodomains Is Critical for JAK Activation. *Cell* (2016) 166(4):920-934