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 : **U1024** **Intitulé Equipe :** **Cilia biology and neurogenesis** **ED d'appartenance :** **ED3C** **Responsable de l'Equipe :** **Nathalie Spassky**	**Responsable du Stage :** **Nathalie delgehyr** **Contacts** Adresse : 46 rue d'Ulm 75005 Paris Email : delgehyr@bio.ens.psl.eu Tel : 0144323715

Titre du projet : **Ependymal fate choice: Role of mechanical stress on the nucleus**

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

Forces applied on cells are transmitted to the nucleus through the LINC complex that links the nucleoskeleton to the actin cytoskeleton. Mechanical forces experienced by the nucleus alter gene expression. **Thus, tension applied to the nucleus via the actin cytoskeleton may drive cell fate**.

Ependymal cells (ECs) and neural stem cells (NSCs) are sister cells, acquiring their own identity late after division. NSCs are reactivable quiescent neuronal progenitors. ECs are multiciliated, postmitotic cells located along brain ventricles, forming a protective barrier and contributing to the cerebrospinal fluid flow. A master regulator, GemC1, interacting with E2F4, and cell cycle related factors (Cdk1/2) promote differentiation. What triggers the activation of these different factors is unknown.

At the onset of EC differentiation, we observed that nuclei undergo massive changes, concomitant with an increase of actin. By analyzing differentiation directly in the brain, we show that inhibiting the Arp2/3 complex, a nucleator of actin, or severing the link between the nucleus and the cytoskeleton impair nuclear deformation and differentiation. Drugs blocking the signalization induced by nuclear deformation also hinders differentiation. Conversely, deforming the nucleus by confining the cells increases differentiation.

We will investigate **the mechanisms leading to differentiation following nuclear deformations** by concentrating on the YAP pathway and the G1/ S transitions factors, as both depend on nuclear deformations and are involved in EC differentiation.

To do so, we will modify them in mouse models, using depletion or overexpression of relevant proteins, and assess the consequences of these modifications on the differentiation. We will analyze their role *in vitro* by mechanically inducing nuclear deformations on cells in culture or purified nuclei and assessing the consequences on gene expression. This project will be performed in the laboratory of Nathalie Spassky **(IBENS)** under the direct supervision of a researcher: Nathalie Delgehyr.

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

- Mahuzier A, et al.. Ependymal cilia beating induces an actin network to protect centrioles against shear stress. **Nat Commun.** 2018 Jun 11; 9(1): 2279.
- **Delgehyr N**, et al.. Ependymal cell differentiation, from monociliated to multiciliated cells. **Methods Cell Biol.** 2015; 127:19-35
- Jord AA, et al.. Centriole amplification by mother and daughter centrioles differs in multiciliated cells. **Nature**. 2014 Dec 4; 516(7529):104-7
- Jord AA, et al.. Calibrated mitotic oscillator drives motile ciliogenesis. **Science.** . 2017 Nov 10;358(6364):803-806.