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

Parcours : **Biologie et Développement Cellulaires 'BDC'**
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Fiche de Projet de Stage M2, Année 2021-2022

Unité INSERM U1163 – Institut Imagine **Intitulé Equipe :** Embryology and Genetics of Congenital Malformations **ED d'appartenance :** BIOSPC **Responsable de l'Equipe** : Pr Jeanne Amiel	**Responsable du Stage :** Dr Sophie Thomas **Contacts** Adresse : 24, Boulevard du Montparnasse 75015 PARIS France Email : sophie.thomas@inserm.fr Tel : 0 1 42 75 43 10

Titre du projet : Functional characterization of a novel centrosomal gene responsible for neocortical malformations

Résumé du Projet de Stage :
Primary cilia (PC) are highly conserved organelles consisting of a microtubule-based axoneme emerging from a basal body derived from the mother centriole and ensheathed by the ciliary membrane. They are required for the transduction of various extracellular signals including the **Sonic Hedgehog** signaling pathway.
PC as well as **centrosomes** from which they nucleate have been shown crucial for **cerebral cortical development**. They are present on all neural stem and progenitor cells (NSPC) present during cerebral cortical development and have been shown crucial for both NSPC expansion, fate determination and neuronal migration.
Using a multifaceted approach integrating **genetics, neurohistopathology and human IPS cell-based models** (cerebral organoids), we aim to uncover and functionally characterize novel candidate genes by dissecting centrosome and PC involvement to the pathophysiological mechanisms underlying cerebral cortical malformations.
In this view, whole exome sequencing analysis allowed us to identify a novel candidate gene encoding a centrosomal protein. *De novo* truncating mutations were identified in 6 cases from 5 distinct families. IPS cells from 4 cases are now being reprogrammed into **IPS cells** and isogenic control IPS cells will be generated by using CRISPR/Cas9 technology that we have now set up in the lab. Mutated and rescued IPS cells will be used to generate complementary 2D and 3D cell-based models of neocortical development, i.e. **neural rosettes** and **cerebral organoids**. By combining last generation imaging analysis (lightsheet and confocal microscopes) as well as RNAseq analysis, those relevant and powerful models should allow us to dissect the pathophysiological mechanisms underlying cerebral cortical malformations associated to centrosomal and PC dysfunction.

Publications de l'équipe relatives au projet de stage (max 5)
-Boutaud L et al, under review. 2D and 3D patient cell-based models to dissect primary cilium involvement to the pathophysiology of malformations of neocortical development.
-**Thomas S et al, Biol Cell. 2019 Sep;111(9):217-231**. Cilia in hereditary cerebral anomalies
-**Le TL et al, Am J Hum Genet. 2020 Jun 4;106(6):779-792**. Bi-allelic Variations of *SMO* in Humans Cause a Broad Spectrum of Developmental Anomalies Due to Abnormal Hedgehog Signaling.
-**Putoux A, et al. Hum Mol Genet. 2019 Mar 15;28(6):877-887.** Altered GLI3 and FGF8 signaling underlies acrocallosal syndrome phenotypes in Kif7 depleted mice.
- **Alby C, et al, Am J Hum Genet. 2015 Aug 6;97(2):311-8.** Mutations in *KIAA0586* Cause Lethal Ciliopathies Ranging from a Hydrolethalus Phenotype to Short-Rib Polydactyly Syndrome.