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

Parcours : **Biologie et Développement Cellulaires 'BDC'**
http://www.master2bdc.fr/
Fiche de Projet de Stage M2, Année 2021-2022

Unité INSERM ou CNRS ou Université : **U1163 Institut Imagine** Intitulé Equipe : **Génétique des troubles du Neurodéveloppement** ED d'appartenance : **BioSPC** Responsable de l'Equipe : **Vincent Cantagrel**	**Responsable du Stage : Marion Coolen** **Contacts** Adresse : 24 Boulevard du Montparnasse 75105 PARIS Email : **marion.coolen@inserm.fr** Tel :**01 42 75 43 66**

Titre du projet : Modeling neurodevelopmental cerebellar disorders using Zebrafish

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

Our laboratory investigates **neurodevelopmental disorders** of the **cerebellum**, a brain region mostly known for its central role in motor coordination and learning. Among those, structural birth defects, or cerebellar malformations, arise early in development and typically affect both the cerebellum and additional parts of the brainstem. They result in devastating neurological disorders, as these structures notably control vital functions such as swallowing and breathing. Other pathologies, such as cerebellar ataxias, involve neuronal degeneration during childhood. Whole-exome and -genome sequencing analyses conducted by our laboratory led to the identification of **new candidate variants** implicated in cerebellar malformations or early-onset ataxias. But we need to validate the pathogenicity of the identified mutations and understand how they lead to the disease. The objective of the Master project will be to tackle this issue, using an animal model amenable to fast **in vivo genetics** studies, the **zebrafish**. **Zebrafish mutant alleles** mimicking the patients' mutations will be generated using **CRISPR/Cas9-mediated genome editing**. For de novo variants, their expression will be targeted specifically to neuronal populations, using previously validated **transgenic driver constructs**. These models will be used to confirm and precisely delineate the deleterious impact of identified variants on the **establishment of cerebellar structure and circuits**. They will also allow us to unravel the **molecular pathways affected**. Different approaches will be deployed including **fluorescent immunohistochemistry and in situ hybridization, 3D imaging, live imaging and transcriptomics**. Altogether this project will lead to the validation of novel genetic variants and gather crucial knowledge on cerebellar development to improve diagnosis and propose innovative therapeutic strategies.

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

Ucuncu, E. et al. MINPP1 prevents intracellular accumulation of the chelator inositol hexakisphosphate and is mutated in Pontocerebellar Hypoplasia. Nat. Commun. 11, 6087 (2020).
Chemin, J. et al. De novo mutation screening in childhood-onset cerebellar atrophy identifies gain-of-function mutations in the CACNA1G calcium channel gene. Brain J. Neurol. 141, 1998–2013 (2018).
Medina-Cano, D. et al. High N-glycan multiplicity is critical for neuronal adhesion and sensitizes the developing cerebellum to N-glycosylation defect. eLife 7, (2018).
Megahed, H. et al. Utility of whole exome sequencing for the early diagnosis of pediatric-onset cerebellar atrophy associated with developmental delay in an inbred population. Orphanet J. Rare Dis. 11, 57 (2016).
Katz, S. *et al.* A Nuclear Role for miR-9 and Argonaute Proteins in Balancing Quiescent and Activated Neural Stem Cell States. *Cell Rep.* **17**, 1383–1398 (2016).