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, 2026-2027

Unité INSERM ou CNRS ou Université : **Institut Imagine U1163** **Intitulé Equipe : Developmental Brain Disorders** **ED d'appartenance : BioSPC** **Responsable de l'Equipe : Vincent Cantagrel**	**Responsable du Stage :** **Marion Coolen** **Contacts** Adresse : 24 Bd du Montparnasse 75015 PARIS Email : marion.coolen@inserm.fr Tel : +33 (0) 1 42 75 43 66

Titre du projet :
From patient mutations to cerebellar circuits: modelling rare neurodevelopmental disorders in zebrafish

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

Rare neurodevelopmental disorders of the cerebellum cause severe neurological symptoms in affected patients, often children, and currently lack effective treatments. They represent a heterogeneous group of diseases, ranging from structural malformations present from birth to progressive ataxias beginning in early childhood. Understanding their genetic and molecular underpinnings is both a scientific challenge and a prerequisite for therapeutic progress.
Our laboratory works at the **intersection of human genetics and developmental neuroscience**. Using whole-genome sequencing in patient cohorts, we have identified in recent years several new candidate variants implicated in cerebellar malformations or early-onset ataxias[1–4]. Yet, precisely how they lead to disease largely remains to be explored.
This master project will investigate the in vivo consequences of identified patient mutations using **zebrafish** as a model organism. Zebrafish are particularly well-suited for this type of study: their nervous system develops rapidly and is directly accessible, and their genome can be edited with precision. Mutant lines carrying mutations mimicking variants found in some patients have already been generated using CRISPR-based genome editing, and are now ready for **functional characterization**. We will examine brain architecture, cellular identity and circuit organization using immunohistology and 3D confocal imaging, complemented by behavioural assays to evaluate the functional consequences at the organismal level. To retrace **the developmental origin** of the defects, we will also investigate how these mutations affect key neurodevelopmental processes, such as neural progenitor dynamics, neuronal fate specification, and cell migration.
Together, these approaches will **connect specific genetic variants to cellular and circuit-level phenotypes**, contributing to a mechanistic understanding of these disorders and informing future diagnosis and therapeutic strategies.

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

1. Bertola, N. et al. Dominant and recessive ATOH1 variants cause distinct neurodevelopmental disorders with hearing loss. Am. J. Hum. Genet. 113, 342–361 (2026).
2. Qebibo, L. et al. The characterization of new de novo CACNA1G variants affecting the intracellular gate of Cav3.1 channel broadens the spectrum of neurodevelopmental phenotypes in SCA42ND. Genet. Med. Off. J. Am. Coll. Med. Genet. 27, 101337 (2025).
3. Coolen, M. et al. Recessive PRDM13 mutations cause fatal perinatal brainstem dysfunction with cerebellar hypoplasia and disrupt Purkinje cell differentiation. Am. J. Hum. Genet. 109, 909–927 (2022).
4. 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).