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, 2025-2026

Unité INSERM ou CNRS ou Université : **Intitulé Equipe : Genetics of developmental anomalies** **ED d'appartenance :BioSPCs** **Responsable de l'Equipe : Jeanne Amiel**	**Responsable du Stage :** **Emilie Dambroise** **Contacts** Adresse : Institut Imagine 24bd Montparnasse 75015 Paris Email :emilie.dambroise@institutimagine.org Tel :0142754250

Titre du projet : Deciphering the role of FGFR3 in cranial vault and neurogenesis development in Muenke Syndrome

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

Muenke syndrome (MS), caused by the gain-of-function p.Pro250Arg mutation in Fibroblast Growth Factor Receptor 3 (FGFR3), is the most common form of syndromic **craniosynostosis**. It is characterized by a broad and variable phenotype that includes premature **fusion of the coronal sutures**, and **neurodevelopmental impairments**. To date the pathogenic mechanisms underlying MS, particularly those driving craniosynostosis and the relationship between cranial suture formation and brain development, remain poorly understood. Zebrafish represent a valuable system for studying FGF signaling-related craniofacial abnormalities[1]. To decipher the pathophysiology of MS, we have first developed an **Fgfr3 loss-of-function zebrafish**, which enabled to characterize the role of FGFR3 during cranial vault and suture formation[3,4]. Recently we have established a unique **MS zebrafish** displaying craniofacial suture fusions and generated induced pluripotent stem cell (**iPSC**) lines from MS patients.

This project aims to investigate the impact of FGFR3 loss- and gain-of-function mutations on brain development during cranial vault formation. In fact, zebrafish provide a unique opportunity to study brain development from the earliest embryonic stages independently of cranial vault formation, thereby allowing the dissociation of the direct effects of Fgfr3 mutations on neurogenesis from secondary consequences associated with cranial vault abnormalities. To assess the impact of Fgfr3 variants on in vivo brain development before, during, and after cranial vault formation, the student will characterize structural alterations and neurogenesis using three-dimensional imaging of optically cleared brains in both Fgfr3 LoF and Fgfr3 MS zebrafish. These analyses will be complemented by RNAscope and immunohistochemistry using region-specific, neural progenitor, and neuronal markers. In parallel, the student will be in charge to differentiate iPSCs into human neural progenitors to study neurogenesis.

We expect that the results of this project will contribute to our understanding of the pathophysiology of the MS, with the goal of developing new therapeutic strategies for this condition.

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

1. Pereur, R. & Dambroise, E. Insights into Craniofacial Development and Anomalies: Exploring Fgf Signaling in Zebrafish Models. *Curr Osteoporos Rep* **22**, 340–352 (2024).
2. Dambroise, E. *et al.* Fgfr3 is a positive regulator of osteoblast expansion and differentiation during zebrafish skull vault development. *J. Bone Miner. Res.* https://doi.org/10.1002/jbmr.4042 (2020) doi:10.1002/jbmr.4042.
3. Pereur, R. *et al.* Cranial suture integrity is maintained by Fgfr3 in zebrafish. Preprint at https://doi.org/10.1101/2025.04.09.647929 (2025) Accepté dans Bone Res. May 2026.