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 ou CNRS ou Université : **Institut Cochin, INSERM U1016, CNRS UMR 8104, Université de Paris.** **Intitulé Equipe : Développement neuro-musculaire, génétique et physiopathologie** **ED d'appartenance : BioSPC** **Responsable de l'Equipe : Pascal MAIRE**	**Responsable du Stage :** **Evelyne BLOCH-GALLEGO** **Contacts** Adresse : 24 rue du Fbg St-Jacques 75014 Paris Email : evelyne.bloch@inserm.fr Tel : 01 44 41 24 58

Titre du projet : Deciphering cognitive neurodevelopment disorders associated with motor deficiencies: role and partners of TRIO-GEF in the interplay between motor neurodevelopment and myogenesis

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

Bipolar disorder, autism, and intellectual disability are frequent complex **neurodevelopmental disorders**: patients display **cognitive symptoms** often associated with **motor symptoms**. Recent studies in human showed that these disorders shared abnormal neuronal axon growth and connectivity, suggesting potential shared impaired molecular mechanisms of neuronal wiring. Interestingly, such disorders were associated with *de novo* heterozygous mutations in ***Trio*** gene, marking it as a candidate gene for further investigation (Ba et al., 2016, Barbosa et al., 2020). *Trio* encodes for a protein (TRIO) that harbors three catalytical domains, including two guanine-exchange factors (GEF) that activate **RhoA and Rac1 small GTPases**. Recent studies in our team established that *Trio* is involved in various steps of muscle development, in addition to being involved in motoneurons (MNs) clustering, motor TCA and hindbrain development. TRIO acts as a master integrator downstream various **guidance cues** to allow the specific activation of Rho-GTPases, and direct axon outgrowth and neuronal migration during embryogenesis (Backer et al., 2007, 2018).
Complete *trio* loss-of-function in mice is embryonic lethal (O'Brian et al., 2000). Since Trio could affect neuronal or muscular development, we have established in the lab tissue specific **conditional knock-out mice** where *trio* is inactivated in (i) differentiated muscle cells or (ii) developing neurons. A comparative phenotypical analysis of the complete KO (-/-) and these conditional mutants will provide clues to better understand the contribution of muscle versus neuron in the phenotype and in physiological roles of TRIO.
As data from the literature and our preliminary data suggest that **inflammation during pregnancy** could reveal neuronal wiring disorders when associated to heterozygous mutations for Rho GTPases activation we will also study the effect of gestational inflammation in heterozygous mice, that are viable, to analyze whether phenotypic features are worsened by inflammation and could mimick phenotypes reported in children with Trio heterozygous mutations.

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

(1) Couesnon, A . ...and **Bloch-Gallego E**. 2013. CLIPR-59, a protein essential for neuro-muscular juncion stability during mouse late embryonic development. Development, 140(7):1583-93.**(2) Bloch-Gallego, E. (**2015) Mechanisms controlling neuromuscular junction stability. Cell Mol Life Sci. 72(6):1029-43 **(3)** Backer, S, ...and **Bloch-Gallego, E.** 2018. Trio GEF mediates RhoA activation downstream of Slit2 and coordinates telencephalic wiring Development. doi: 10.1242/dev.153692. **(4)** Dos Santos M, ...and **Maire P**. 2020. Single-nucleus RNA-seq and FISH identify coordinated transcriptional activity in mammalian myofibers Nat Commun. doi: 10.1038/s41467-020-18789-8 **(5)** Wurmser M, ...and **Maire P**. SIX 1 and SIX4 homeoproteins regulate PAX7+ progenitor cell properties during fetal epaxial myogenesis. Development. 2020 Oct doi: 10.1242/dev.185975.