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

Parcours : **Biologie et Développement Cellulaires 'BDC'**

http://www.master2bdc.fr/

Fiche de Projet de Stage de M2, 2022-2023

Unité INSERM, CNRS ou Université : UMR861, I-Stem **Intitulé Equipe :** Motoneuron **Responsable de l'Equipe :** MARTINAT	**Responsable du Stage :** **Martinat Cécile** **Contacts** cmartinat@istem.fr

Titre du projet : Use of human pluripotent stem cells to decipher the mechanisms underlying the selective vulnerability of motor neurons in Spinal Muscular Atrophy

Résumé du Projet de Stage (en 300 mots maximum, mots clés en gras)
Spinal muscular atrophy is an autosomal recessive disease caused by a deficiency of the ubiquitously expressed survival of motor neuron protein. While spinal motoneurons are highly vulnerable, some motor neuron groups, including cranial motoneurons, which innervate the face and eye muscles, are spared. Understanding the mechanisms underlying this selective vulnerability is crucial to determine how the loss of a ubiquitously expressed protein can induce degeneration in a select cell type and consequently to determine new therapeutic pathways. However, progresses towards identification of such mechanisms have been hampered by the restricted access to these cellular types in humans.
This project aims to address this probelm by using human pluripotent stem cells derived from SMA patients. By taking advantage of the capacity to differentiate these cells into the main cell types involved in neuromuscular communication, the specific objectives of this project are twofold:
1). To decipher the molecular mechanisms that may be at the origin of the specific damage of spinal motor neurons. This first objective will be based on a recent transcriptomic analysis perfomed by the team that aimed at identifying genes differentially expressed between spinal motor neurons, which degenerate in SMA and cranial motor neurons, that do not show any alteration of their survival despite the fact that they express the mutation. Validation experiments by RTqPCR and Western blot will be conducted to assess the molecular pathways that may be responsible for this different vulnerability.
2). To evaluate the functional consequences of these molecular mechanisms using a co-culture system already debeloped in the laboratory between hiPSC-derived motoneurons and their skeletal muscle targets.
In a longer term, this project aims at evaluating the possibility to capture in vitro the slective vulnerability associated with SMA and should facilitate the identification of new therapeutic targets toward preserving vulnerable motoneurons.

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

1. D'Amico D, Biondi O, Januel C, Bezier C, Sapaly D, Clerc Z, El Khoury M, Sundaram VK, Houdebine L, Josse T, Della Gaspera B, Martinat C, Massaad C, Weill L, Charbonnier F. (**2022**). Activating ATF6 in spinal muscular atrophy promotes SMN expression and motor neuron survival through the IRE1alpha-XBP1 pathway. **Neuropathology and applied neurobiology**: e12816. 10.1111/nan.12816
2. Merien A, Tahraoui-Bories J, Cailleret M, Dupont JB, Leteur C, Polentes J, Carteron A, Polveche H, Concordet JP, Pinset C, Jarrige M, Furling D, Martinat C. (**2021**). CRISPR gene editing in pluripotent stem cells reveals the function of MBNL proteins during human in vitro myogenesis. **Hum Mol Genet** 31: 41-56. 10.1093/hmg/ddab218
3. de Lamotte JD, Polentes J, Roussange F, Lesueur L, Feurgard P, Perrier A, Nicoleau C, Martinat C. (**2021**). Optogenetically controlled human functional motor endplate for testing botulinum neurotoxins. **Stem cell research & therapy** 12: 599. 10.1186/s13287-021-02665-3

4. Powis RA, Karyka E, Boyd P, Come J, Jones RA, Zheng Y, Szunyogova E, Groen EJ, Hunter G, Thomson D, Wishart TM, Becker CG, Parson SH, Martinat C, Azzouz M, Gillingwater TH. (**2016**). Systemic restoration of UBA1 ameliorates disease in spinal muscular atrophy. **JCI insight** 1: e87908. 10.1172/jci.insight.87908
5. Maury Y, Come J, Piskorowski RA, Salah-Mohellibi N, Chevaleyre V, Peschanski M, Martinat C, Nedelec S. (**2015**). Combinatorial analysis of developmental cues efficiently converts human pluripotent stem cells into multiple neuronal subtypes. **Nat Biotechnol** 33: 89-96.