Ecole Doctorale COMPLEXITE DU VIVANT – Fiche Projet CONCOURS

Fiche à nommer selon le format Nom_Prénom_ProjetED19, à enregistrer en format PDF et à renvoyer à l'adresse: edcdv@upmc.fr.

Nom et prénom du directeur de thèse (et si besoin du co-directeur) : Pr. Bertrand Fontaine
Le directeur de thèse et le co-directeur doivent impérativement avoir l'HDR ou équivalent
Coordonnées   Tel : 01 40 77 81 58   e-mail : bertrand.fontaine@upmc.fr

Nom et prénom du co-encadrant (non HdR) (s'il y a lieu) : Stéphanie Godard-Bauché
Coordonnées   Tel : 01 40 77 96 44
   e-mail : stephanie.godard-bauche@upmc.fr

Y-a-t-il un candidat déjà identifié pour le projet:   OUI   NON

Nom et prénom du responsable de l'équipe : Pr. Bertrand Fontaine & Dr. Laure Strochlic
Intitulé de l'équipe : Connectivité neuromusculaire en santé et pathologies (NMConnect)
Nombre de chercheurs et enseignants-chercheurs statutaires de l’équipe titulaires d’une HDR (ou équivalent) : 2

Nom et prénom du responsable d'UMR ou de département: Pr. Bertrand Fontaine
Intitulé et N° d'UMR ou de département: UMRS974, Centre de recherche en Myologie
Signature du directeur d'UMR ou de département (vaut avis favorable pour le dépôt du projet) : 

[signature]
Neuromuscular junctions (NMJs) are highly specialized chemical synapses that allow motor nerves to convey their signals to their target muscle fibers by a temporally fine-tuned balance of distinct signaling activities. Any disruption of these signaling activities drastically affects NMJ formation that can result in severe diseases of the NMJ such as congenital myasthenic syndroms (CMS). CMS are a heterogeneous group of genetic assignments of malfunction of neuromuscular transmission. These are rare neuromuscular diseases characterized by localized or generalized muscle weakness and fatigue. The severity of the clinical signs is variable, ranging from brutal respiratory distress that occurs at birth to more moderate symptoms starting in adulthood, suggesting that some mutations preferentially affect proteins essential for synaptogenesis, while others affect proteins required for the maintenance/function of the neuromuscular synapse.

In recent decades, the development of reverse genetics has led to the identification of over 30 causative CMS genes. Despite the high number of discovered genes, a significant proportion of patients with a possible diagnosis of CMS are genetically uncharacterized. The disease mechanisms remain unresolved in part due to the lack of knowledge of the cellular and molecular processes involved and the subsequent inability to perform mechanistic studies. Thus, a better understanding of the functional interplay of signaling networks underlying NMJ connectivity is a necessity to decipher the pathophysiological mechanisms in order to develop new therapeutic strategies.

The receptor complex formed by MuSK (muscle specific kinase) and Lrp4 (LDL receptor-related protein 4) a member of the Low-Density Related Protein family, expressed in the middle of the muscle fibers, constitutes the central scaffold that orchestrates both NMJ formation and maintenance from the postsynaptic side. The main goal of this PhD project is to investigate 1) the pathophysiological mechanisms (morphological and functional impact on neurotransmission) of newly identified genetic mutations coding for core components of the MuSK/Lrp4 signaling pathway in the French CMS cohort and 2) explore the modulation of MuSK activity as an approach to restore appropriate synaptic connectivity in a pathological context.

To realize this project the selected candidate will use a wide range of techniques of molecular and cellular biology (cell culture, adeno-associated virus particles delivery of cDNAs), biochemistry, imaging (confocal and electronic microscopy) and electrophysiology both in vitro in muscle cells and in vivo in CMS-modeling mouse models available in the laboratory.
The team Neuromuscular connectivity in health and diseases directed by Pr. Fontaine and Dr. Strochlic has a long standing expertise in the neuromuscular field, developed unique NMJ disease modeling models and works in close collaboration with the Paris Est French reference center for neuromuscular diseases which is among the largest clinical reference centers in Europe, facilitating access to human neuromuscular diseases. One of the main goal of the team is to study the neuromuscular synapse using human genetic diseases related to distinct deficiencies of the neuromuscular transmission such as CMS (synaptic transmission) and channelopathies (muscle excitability). In order to respond to patient’s expectation for efficient treatment, our group decided to imply itself deeper in translational research, a step closer to patient diagnosis and drug discovery. Using our clinical expertise, our national networks such as RESOCANAUX and CMS which have allowed us to constitute large cohorts of patients with CMS, muscle channelopathies and related diseases, we have set up a well-established and successful strategy to identify/study new causative genetic mutations and to explore the underlying pathophysiological mechanisms (Bauché et al., 2017; 2016).

Most of the technological and methodological aspects of this PhD project are mastered and controlled by the team. All the mouse lines are being handled in approved facilities on site and the experimental procedures will be conducted in accordance with the European guidelines for care and use of experimental animals. Vectorology, electrophysiology and imaging are available through core facilities on site. The selected candidate will be trained to several state-of-the-art technics under the supervision of a research engineer from Sorbonne University.

Thèses actuellement en cours dans l’équipe

*Tous les encadrements doivent être indiqués (y compris les co-directions avec un autre HDR pour des doctorants d’une autre ED, et les encadrements dans le cadre de programmes doctoraux tels qu’IPV, FDV...)*

<table>
<thead>
<tr>
<th>Nom et Prénom du doctorant</th>
<th>Directeur(s) de thèse</th>
<th>Année de 1ère inscription</th>
<th>ED</th>
<th>Financement</th>
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<tr>
<td>Myriam Boëx</td>
<td>Dr. Laure Strochlic</td>
<td>2016</td>
<td>CDV, ED515</td>
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Trois publications récentes du directeur de thèse (du co-directeur ou du co-encadrant s’il y a lieu). Mettre en gras le nom du directeur de thèse.


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**Docteurs encadrés par le directeur de thèse** ayant soutenu entre la date de dépôt de ce dossier et il y a 5 ans et publications relatives à leur sujet de thèse. Mettre en gras le nom du directeur de thèse et celui du docteur.

<table>
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<tr>
<th>Nom Prénom</th>
<th>Date de soutenance</th>
<th>Durée de thèse (en mois)</th>
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<tr>
<td>Damotte Vincent</td>
<td>2013</td>
<td>36</td>
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**Publications**:
