PROPOSITION SUJET DE THESE

Concours d'attribution des Contrats Doctoraux 2019 – 2022
A renvoyer impérativement **avant le 2 mars 2019** par courriel au format **PDF** à edsvs-direction@univ-amu.fr

1. Choix du sous-jury (vous ne pouvez cocher qu'une seule case) :

☐ JURY 1 – Biologie Cellulaire (Développement – Immunologie – Biologie Végétale – Physiologie).

☐ JURY 2 – Microbiologie – Génomique (Bioinformatique – Biochimie Structurale – Biochimie).

☐ JURY 3 – Neurosciences (Neurobiologie cellulaire – Neurosciences Cognitives et Comportementales – Neuroimagerie – Neurosciences Computationnelles).

☒ JURY 4 – Biologie Santé (Oncologie – Cardiovasculaire – Santé Publique – Maladies Infectieuses – Génétique).

Laboratoire	
Nom et N° :	Marseille Medical Genetics (INSERM U1251)
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Nombre d'HDR dans l'équipe	4
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HDR obtenue le :	10 février 2012
Nom du Codirecteur éventuel :	
Nom(s) du(es) doctorant(s) en cours d'encadrement :	
Nom et date de soutenance du précédent doctorant encadré :	Pauline HEUX (21 novembre 2017)
Publication du Doctorant :	https://www.ncbi.nlm.nih.gov/pubmed/29316344

Résumé du projet de thèse (**420 mots max**) :

Characterization of mosaic congenital neurocristopathies

Birth defects affecting derivatives of the stem cell population known as the neural crest are known collectively as neurocristopathies (https://hal.archives-ouvertes.fr/hal-01851974). These are often congenital syndromes, where more frequent forms preferentially affect the palate, eyes or heart, but dozens of rarer diseases also impact

disseminated systems such as the skin or the peripheral nervous system. While the genetic underpinnings of many specific rare neurocristopathies over the last decade have been discovered, most remain without molecular diagnosis and are relatively poorly defined as clinical entities.

Our group and others have recently shown that a subset of cutaneous malformation syndromes of blood vessels and/or pigment cells, predisposing to lethal complications, are due to recurrent post-zygotic mutations found in many adult cancers. These new somatic mutations lead to constitutive activation, in a mosaic manner, of intracellular enzymes that transduce growth factor signaling. Based on preliminary data from our mouse models, we hypothesize that additional human birth defects result from expression of the same mutations in multipotent neural crest derivatives, affecting not only their progeny in the skin but also in the heart or skull.

The Ph.D. candidate will:

- Complete the phenotypic and molecular characterization of our mouse models after inducing conditional timed activation of three intracellular effectors within all or a subset of the neural crest lineage;
- In collaboration with physicians from Marseille's Timone Hospital and beyond, participate in our analyses of gene sequencing projects to demonstrate new mutations affecting these pathways in candidate birth defects, based in part on the murine phenotypes;
- Develop paired clonal induced pluripotent cell lines directly from patient tissues bearing or not known somatic mutations in each effector, which experiments we have already begun. The goal is to differentiate these into neural crest and then specific cardiovascular, sensory or pigment derivatives, in order to show differential responses to the mutations;
- Conduct transcriptome and secretome analyses on differentiated cells or explants from these models, to identify pharmacological agents that may counteract the downstream lineage-specific and non-cell-autonomous effects *in vitro*. The ultimate aim is to use the data from these studies *in vivo* to establish proof-of-concept in reversing or preventing undesirable clinical outcomes.

The ideal candidate has some experience or a demonstratable interest in learning relevant techniques in lineage tracing, histology, cell culture, molecular biology including RNA /protein identification, and/or bioinformatics, and can already read English comfortably. Vaccination against hepatitis B, diptheria, tetanus and polio is a requirement. The candidate will obtain certification to work directly with mice, an integral part of the project.

ATTENTION : les porteurs de projet ayant obtenu un Contrat Doctoral lors de la session de juin 2018 ne sont pas éligibles au concours 2019.