ÉCOLE DOCTORALE UNIVERSITÉ PARIS-EST
Sciences de la Vie et de la Santé

Campagne de recrutement 2020

Titre du projet de Thèse
Cellular origin of spine deformity in a new murine model of Neurofibromatosis type 1

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Unité / laboratoire d'accueil

Intitulé de l'unité/laboratoire : INSERM U955-Equipe « Biologie du système neuromusculaire », Groupe Colnot

Nom du Directeur de l'unité / laboratoire d'accueil : Frédéric Relaix

Contexte scientifique du projet et objectifs (0,5 page maximum)

Arial 11, interligne simple

Scoliosis, a condition characterized by spine deformity, affects 3% of the population and is more prevalent in adolescents. The majority of scoliosis cases are idiopathic and other cases can be associated with genetic disorders such as neurofibromatosis type 1 (NF1). NF1 is an autosomal dominant condition affecting 1 in 3000 individuals and due to inactivating mutations in the *NF1* gene, encoding the tumor suppressor RAS-GTPase-activating protein neurofibromin. NF1 patients can be affected by a variety of symptoms such as skin lesions, neurofibromas, learning disabilities and several orthopaedic manifestations including pseudarthrosis, osteoporosis and scoliosis with no genotype-phenotype correlation and no effective treatment options reported so far. Several reports have shown that somatic NF1 mutations or "second hit" leading to double inactivation of NF1 in specific cell lineages may be associated with these various manifestations.
The goal of this project is to determine the cellular origin of spine deformity in a new mouse model of NF1 mimicking several aspects of the human pathology including bone manifestations (Radomska et al., 2019). The first aim will be to perform a detail phenotypic characterization of spine deformity mutant mice. The second aim will be to determine the role of the cell lineage involved in spine deformity in the mouse model. The third aim will be to perform molecular and cellular analyses of tissue samples from NF1 patients affected with scoliosis in order to better correlate the findings between the animal model and human pathology. The project will use a wide range of approaches and techniques including in vivo mouse phenotypic analyses, imaging techniques, primary cell cultures, flow cytometry and molecular analyses used in the Colnot group in collaboration with the group of Piotr Topilko at IMRB.

https://colnotgroup.wixsite.com/home

Radomska, K.J., Coulpier, F., Gresset, A., Schmitt, A., Debbiche, A., Lemoine, S., Wolkenstein, P., Vallat, JM., Charnay, P. and Topilko P. Cellular origin, tumor progression, and pathogenic mechanisms of cutaneous neurofibromas revealed by mice with Nf1 knockout in boundary cap cells. Cancer Discovery, 9, 130-147 (2019)

Compétences requises du candidat (5 lignes maximum)

Arial 11, interligne simple

Motivated, curious, passionate about science.
Well-organized, rigorous, good experimentalist.
Ability to interact with others, to work in a team.
Training in cellular and molecular biology.
Experience with animal experimentation (mice) preferred.

Publications de l'équipe d'accueil de ces 5 derniers années en lien avec le projet (5 publications maximum)

1- Duchamp de Lageneste, O, Julien, A, Abou-Khalil, R, Frangi, G, Carvalho, C, Cagnard, N, Cordier, C, Conway, SJ and Colnot, C. Periosteum contains skeletal stem cells with high bone regenerative potential controlled by Periostin. Nature Communications, 2018 Feb 22;9(1):773. PMID:29472541
2- Abou-Khalil, R, Yang, F, Lieu, S, Julien, A, Perry, J, Pereira, C, Relaix, F., Miclau, T, Marcucio, R and Colnot, C. Role of muscle stem cells during skeletal regeneration, Stem Cells, 2015, May;33(5):1501-11. PMID: 25594525

3- Stanzou A, Schirwis E, Swist S, Alonso-Martin S, Polydorou I, Zarrouki F, Mouisel E, Beley C, Julien A, Le Grand F, Garcia L, Colnot C, Birchmeier C, Braun T, Schuelke M, Relaix F, Amthor H. BMP signaling regulates satellite cell-dependent postnatal muscle growth. Development, 2017 Aug 1:144(15): 2737-47. PMID: 28694257

4- Wang L, Hsiao EC, Lieu S, Scott M, O'Carroll D, Urrutia A, Conklin BR, Colnot C, and Nissenson RA. (2015) Loss of Gi G-Protein-Coupled Receptor Signaling in Osteoblasts Accelerates Bone Fracture Healing. J Bone Miner Res **30**(10): 1896-904 PMID:25917236

5- Abou-Khalil, R, Yang, F, Mortreux, M, Lieu, S, Yu, YY, Wurmser, M, Pereira, C, Miclau, T, Marcucio, R and Colnot, C. Delayed bone regeneration is linked to chronic inflammation in murine muscular dystrophy, Journal of Bone and Mineral Research, 2014 Feb;29(2):304-15