INSTITUT DE GÉNOMIQUE FONCTIONNELLE

CNRS UMR5203 - INSERM U1191 - UNIVERSITÉ DE MONTPELLIER

3-year postdoctoral position available in Montpellier - France

We are seeking a highly motivated and skilled candidate for a 3-year (1-year renewable twice) postdoctoral position to characterize, from cellular to behavioral levels, animal models of NALCN-related diseases. The project will be performed in the framework of the RestoreLeak project, funded through the ERA-NET NEURON 2021 call for Transnational Research Projects on Neurodevelopmental Disorders (https://www.neuron-eranet.eu/projects/RestoreLeak/). The candidate will be mentored by Dr Arnaud Monteil, coordinator of RestoreLeak, in Dr Philippe Lory's team ("*Ion channels in neuronal excitability and diseases*", at IGF (https://www.igf.cnrs.fr) Montpellier, France.

Scientific context:

The IHPRF1 (*Infantile, Hypotonia, with Psychomotor Retardation and Characteristic Facies 1*) and CLIFAHDD (*Congenital contractures of the Limbs and FAce, Hypotonia, and Developmental Delay*) syndromes are two severe neurodevelopmental disorders linked to mutations in the *NALCN* gene. The sodium (Na^+) leak channel NALCN is a crucial regulator of cell excitability by setting up the resting membrane potential of neurons and endocrine cells (Cochet-Bissuel et *al*, 2014; Guérineau et *al*, 2021). The IHPRF1 pathogenic variants are inherited autosomal recessive loss-of-function while CLIFAHDD variants are dominant, *de novo* gain-of-function (Chong et *al*, 2015; Bouasse et *al*, 2019). Both syndromes display an onset early in infancy and may lead to premature death. Patients exhibit a large panel of symptoms of variable severity, and there is yet no available treatment. Over the last years, we have developed a wide range of tools (from cell to animal models) to study the role of NALCN in both physiological and pathological conditions. Recently, we have generated animal models that carry NALCN mutations to characterize the corresponding developmental disorders. The first objective of the project will be to characterize the physiological defects in these models. This will first be performed by using a combination of techniques including, but not restricted to, electrophysiological recordings (EEG, patch-clamp), calcium imaging, hormone release measurement, and at the behavioral levels using motor/cognitive tests. In a second step, gene therapy approaches will be assessed in those animal models to make the proof of principle that they represent relevant therapeutic strategies to restore normal phenotypes.

Essential Requirements

- PhD or MD/PhD with a background in Physiology and/or Neuroscience
- Excellent research records and academic activities
- Strong expertise in wet-lab experience with advanced techniques (i.e., Patch-clamp, Viral-mediated gene transfer in animal models, Calcium imaging) and quantitative data analysis
- Experience in mouse behavior assessment and analysis is a pre-requisite. Holding an EU accreditation to conduct experiments in animals will be a plus.
- Be imaginative, open, dynamic, team-worker, strongly self-driven and well organized.

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Scientific environment:

The lab '**I**nstitut de **G**énomique **F**onctionnelle' (IGF, *Institute of Functional Genomics*) is a multidisciplinary Research Center dedicated to studies of the physiological and pathological cellular communications in neurobiology, endocrinology, oncology and cardiology. It gathers about 250 researchers, engineers and technicians, and provides a dynamic and challenging environment, with access to high-level technological facilities. The candidate will benefit from a stimulating, interactive and collaborative research environment, as well as an access to state-of-the-art facilities from the BioCampus Service Unit (https://www.biocampus.cnrs.fr).

Salary:

Net income: 2100-2200 € /month

How to apply

Applicants should send an e-mail to Dr. Arnaud Monteil (arnaud.monteil@igf.cnrs.fr) with a CV including a list of publications and technical expertise, a description of research interests and at least two names of individuals willing to act as references for the candidate.

Application review will begin immediately and will continue until a suitable candidate is selected. The position will preferentially start July 1st, 2022

Most relevant references related to the topic from the hosting laboratory

Impheng H, Lemmers C, Bouasse M, Legros C, Pakaprot N, Guérineau NC, Lory P, **Monteil A**. (2021) The sodium leak channel NALCN regulates cell excitability of pituitary endocrine cells. *FASEB J.* 35(5): e21400. doi: 10.1096/fj.202000841RR.

Milman A, Ventéo S, Bossu JL, Fontanaud P, **Monteil A**, Lory P, Guérineau NC. (2021) A sodium background conductance controls the spiking pattern of mouse adrenal chromaffin cells in situ. *J Physiol*. Jan 15. doi: 10.1113/JP281044.

Bouasse M, Impheng H, Servant Z, Lory P, **Monteil A**. (2019) Functional expression of CLIFAHDD and IHPRF pathogenic variants of the NALCN channel in neuronal cells reveals both gain- and loss-of-function properties. *Sci Rep.* Aug 13;9(1):11791. doi: 10.1038/s41598-019-48071-x.

Chong JX, McMillin MJ, Shively KM, Beck AE, Marvin CT, Armenteros JR, Buckingham KJ, Nkinsi NT, Boyle EA, Berry MN, Bocian M, Foulds N, Uzielli ML, Haldeman-Englert C, Hennekam RC, Kaplan P, Kline AD, Mercer CL, Nowaczyk MJ, Wassink-Ruiter JS, McPherson EW, Moreno RA, Scheuerle AE, Shashi V, Stevens CA, Carey JC, **Monteil A**, Lory P, Tabor HK, Smith JD, Shendure J, Nickerson DA; University of Washington Center for Mendelian Genomics, Bamshad MJ (2015) De Novo Mutations in NALCN Cause a Syndrome Characterized by Congenital Contractures of the Limbs and Face, Hypotonia, and Developmental Delay. *Am J Hum Genet*. 96(3):462-73.

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Swayne LA, Mezghrani A, Varrault A, Chemin J, Bertrand G, Dalle S, Bourinet E, Lory P, Miller RJ, Nargeot J, **Monteil, A**. (2009) The NALCN ion channel is activated by M3 muscarinic receptors in a pancreatic beta-cell line. *EMBO Rep.* **10**, 873-880.

Reviews:

Guérineau NC, **Monteil A**, Lory P. (2021) Sodium background currents in endocrine/neuroendocrine cells: towards unraveling channel identity and contribution in hormone secretion. *Front Neuroendocrinol.* Sep 27:100947. doi: 10.1016/j.yfrne.2021.100947.

Cochet-Bissuel M, Lory P, **Monteil A** (2014) The sodium leak channel, NALCN, in health and disease. *Frontiers in cellular neuroscience* **8:** 132.

Swayne LA, Mezghrani A, Lory P, Nargeot J, **Monteil A** (2010) The NALCN ion channel is a new actor in pancreatic β-cell physiology. *Islets*, **2**, 53-56.

Snutch TP and **Monteil A** (2007) The sodium "leak" has finally been plugged. *Neuron*, **54**, 505-507.

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