

POSTDOCTORAL POSITION

Group of Pr Piotr Topilko

Deciphering the role of sensory nerves as a novel player governing development of cutaneous neurofibromas in Neurofibromatosis type 1 and an actionable target for their treatment

Institute Mondor of Biomedical Research (IMRB); INSERM U955, Paris, France

The position will be for maximum 3-years starting from January 2023.

We are seeking to hire a highly motivated postdoctoral fellow to work on deciphering the role of sensory innervation in the pathogenesis of cutaneous neurofibromas (cNFs) in Neurofibromatosis type 1. CNFs are benign nerve sheath tumors that develop, often in large numbers, in all patients with neurofibromatosis type 1 (NF1). NF1 belongs to the family of genetic diseases called "RASopathies", is caused by mutations in the NF1 tumor suppressor gene and is characterized by a plethora of symptoms, including a higher incidence of various types of cancers. We have conceived a genetically engineered mouse model that faithfully recapitulates the development of NF1 symptoms, including cNFs. Despite the biallelic loss of NF1 in Schwann cells (SC, cells of origin of cNFs), our observations suggest a pivotal role for sensory innervation in the initiation and development of these tumors both in the mouse model and in NF1 patients. The research of our group covers the various aspects of NF1 tumorigenesis using *ex* and *in vivo* models and NF1 patients. We apply multiomics approaches to decipher the mechanisms governing the successive steps of neurofibroma development, including their malignant transformation and to identify and validate actionable targets for their treatment.

This project aims to explore the role of the cross-talk between sensory neurons and Schwann cells in cNFs from mutant mice and patients. First, by better characterizing the innervation defect in cNFs using IHC and 3D reconstruction of SCs-sensory axons interaction by electron microscopy. Second, by performing fate mapping and transcriptomic analysis, at single cell resolution, of sensory neurons innervating cNFs. Third, by performing genetic and pharmacological ablation of these neurons in the mouse model and exploring the impact of their loss on cNF development. Fourth, by studying the cross talk between NF1 mutant SCs and sensory neurons in the culture dish and finally by exploring the role of CGRP and other neuropeptides overexpressed by sensory nerve terminals as a novel target to prevent or regress CNF. The candidate will also participate in translational research aimed at using novel approaches to prevent or slow the development of CNFs.

The postdoc candidate should have expertise in peripheral neurons biology. Experience in cancer biology and scRNAseq would be appreciated but not required. The postdoc candidate will integrate our young and dynamic team of postdocs, clinicians, engineers and PhD students located at IMRB. The IMRB is one of the main multidisciplinary biomedical research centers in the eastern part of the Paris region. The research teams develop high-level fundamental and translational research in a wide variety of fields, in direct link with health services and a large number of patient cohorts. It brings together nearly 600 people belonging to 14 research teams and 4 technological platforms.

Selected publications of the host team relative to the project:

Radomska, K. J. et al. Cellular Origin, Tumor Progression, and Pathogenic Mechanisms of Cutaneous Neurofibromas Revealed by Mice with Nf1 Knockout in Boundary Cap Cells. *Cancer Discov* **9**, 130-147 (2019).

Gresset, A. et al. Boundary Caps Give Rise to Neurogenic Stem Cells and Terminal Glia in the Skin. *Stem Cell Reports* **5**, 278-290 (2015).

Website: <https://www.imrb.inserm.fr>

Interested candidates should send their CV, a motivation letter including research interests and names of 2 referees to: Piotr.topilko@inserm.fr