POSTDOCTORAL POSITION

Group of Pr Piotr Topilko

Deciphering molecular signatures of pre-malignant lesions in Neurofibromatosis type 1 (NF1)

Institut Mondor of Biomedical Research (IMRB); INSERM U955, Creteil, France

The position will be for maximum 3-years starting from September 2022

We seek to hire a highly motivated postdoctoral fellow to work on exploring genetic, epigenetic and transcriptomic alterations driving malignant transformation in NF1. **Malignant peripheral nerve sheath tumors** (MPNSTs) are aggressive sarcomas with no effective therapy to date. In half of cases, they occur in NF1 patients, a genetic disorder caused by mutations in the *NF1* tumor suppressor gene. NF1 patients develop benign nerve sheath tumors, called plexiform neurofibromas (pNFs), known to arise from the *NF1*$^{-/-}$ Schwann cell (SC) lineage with hyperactive RAS pathway. About 10% of pNFs transform into MPNSTs. This progression is preceded by a pre-neoplastic state, termed as “dysplastic” NF (dNF) and characterized by increased proliferative activity of *NF1*$^{-/-}$ SCs and heavy but transient infiltration by T lymphocytes. The malignant transformation is driven by acquisition by mutant SCs of additional , gain of function, mutations in tumor suppressor genes. Our team has developed a *Nf1*-KO mouse model that successfully recapitulates the development of pNFs and their transformation into MPNSTs through a dysplastic phase. This project aims to **apply multi-omics approach on dNFs issued from this mouse model and from NF1 patients to address key questions concerning molecular events underlying malignant transformation of NFs**. First, by performing biobanking followed by genetic, epigenetic and transcriptomic analyses of tumor cells we expect identifying molecular alterations and candidate genes involved in this process. Next, by grafting individually barcoded tumor cells into nude recipients, and analyzing developing tumors at successive transformation steps, we will rank these molecular modifications, and set up a patient-derived xenograft model for drug screening essays. Last, by grafting tumor cells carrying permanent inactivation of candidate genes, we expect to functionally validate their role in progression of dNFs into MPNSTs. The candidate will also participate in translational research aimed at using ex and in vivo models of malignant transformation to identify molecules capable of preventing or slowing this process.

The Postdoc candidate should have expertise in both cellular and molecular biology applied to cancer. A background in single cell molecular analyses (epigenetics and transcriptomics, coding in R), both experimental procedure and bioinformatic analysis would be appreciated but not required. The post-doc candidate will integrate our young and dynamic team including Postdocs, clinicians, engineers and PhD students located at IMRB. IMRB is one of the major pluridisciplinary biomedical research centres in the eastern part of the Paris region. The research teams develop high-standing basic and translational research in a wide variety of fields in direct connection with healthcare services and a large number of patient cohorts. It comprises almost 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*