Post-doctoral position available

at the Institute for Advanced Biosciences

Laboratory: the team Mechanobiology, Immunity and Cancer, headed by Arnaud Millet MD-PhD (Inserm researcher)
https://iab.univ-grenoble-alpes.fr/Team_MILLET_EN?language=en

Duration: 1 year

Tumour associated macrophages induced chemoresistance in colon cancers

Context: Drug resistance is the main factor explaining failure of treatment in cancer. This resistance could be due to many various mechanisms, which include tumour burden and growth kinetics, tumour heterogeneity, physical barriers, undruggable cancer drivers and the immune microenvironment. One of the major component of this tumour immune microenvironment (TIME) is composed of macrophages that acquired, during tumour progression, a pro-tumoral phenotype and are coined as tumour associated macrophages (TAM) in this context. These macrophages originate largely from the bone marrow, but could also came from the resident macrophage pool. The heterogeneity of TAMs raises the question of microenvironment implication in their resulting phenotype. In order to address that question, we have recently published studies showing how the physical environment could impact the polarization of these cells and found that this environment modifies their activation states more profoundly than previously thought (1,2). In order to understand how this environment could influence TAMs functions we have studied how a hypoxic environment could modulate the response of cancerous cells to chemotherapy in presence of macrophages. We have recently found that hypoxia is able to induce a chemoresistance mechanism to 5FU (5 Fluoro-Uracil) due to macrophages (3).

Description: The objective of the project is to develop a relevant in vivo model in mice to study the importance of hypoxia in macrophage commitment to support tumour growth, notably through the induction of chemoresistance. Our goal is to study the metabolic signature of hypoxic tumour associated macrophages. Due to an epigenetic control, mice macrophages do not resume the metabolic switch present in human macrophages leading to the chemoresistance mechanism identified (3). We will use a developed “humanized” mice macrophage cell line in the team to study the quantitative role of macrophages in chemoresistance in hypoxic areas. To perform this study, we will use an orthotopic colon cancer model in mice.

Expected candidate profile: As the project is at the interface between macrophage’s biology and cancer, the applicant should have prior experience in these research fields. The applicant should have a PhD in immunology, or cell and molecular biology and should be proficient with *in vivo* experiments. A track record (as evidenced by publications in peer-viewed journals) in relevant fields is required. Applicants must be able to fluently communicate in English (oral and written skills). He/she must be able to communicate his/her results to the team.

Candidates must provide a CV, a cover letter stating research interests and qualifications, as well as recommendation letters and references to Dr Arnaud Millet: arnaud.millet@inserm.fr

References:

(1) Court M, Petre G, El-Atifi M, Millet A. Proteomic signature reveals modulation of human macrophage polarization and functions under differing environmental oxygen conditions. Mol Cell Proteomics. 2017 Dec;16(12):2153-2168.

(2) Court M, Malier M, Millet A. 3D type I collagen environment leads up to a reassessment of the classification of human macrophage polarizations. Biomaterials. 2019 Jul; 208:98-109.

(3) Malier M, Court M, Gharzeddine K, , Laverriere MH, Marsili S, Thomas F, Decaens Th, Roth G, Millet A. Hypoxia Drives Dihydropyrimidine Dehydrogenase Expression in Macrophages and Confers Chemoresistance in Colon Cancer. BioRxiv 2020 doi: https://doi.org/10.1101/2020.10.15.341123