2018-02

IC-**3i** International PhD Program

PhD thesis project

2018 Call for application

Long noncoding RNAs as master regulators of intratumoral heterogeneity and tumor progression

General information

Call	2018-2019
Reference	2018-02-MORILLON_PINSKAYA
Keyword(s)	lncRNA, epigenetics, single-cell, transcription, cancer

Director(s) and team

Thesis director(s)	Antonin Morillon
Research team	Non Coding RNA, Epigenetic and Genome Fluidity
Research department	UMR3244 – Dynamics of Genetic Information

Description of the PhD thesis project

Long noncoding (lnc)RNAs play an important role in tumorigenesis, contributing to all hallmarks of cancer. When associated with chromatin modifying complexes lncRNAs were shown to control the whole transcriptional program of the cell thus defining its identity and tumor cell plasticity. However, a growing body of evidence points to high cell-to-cell heterogeneity of lncRNA expression within tumors, suggesting that lncRNAs together with chromatin features may be responsible for cell fate decisions and formation of cellular subpopulations endowed with different stemness, metastasis or drug resistance properties. Using total RNA-sequencing and in-house developed computational pipelines, we recently identified thousands of novel lncRNAs associated with the epithelial-to-mesenchymal transition (EMT) and highly expressed in prostate tumors. In this project, we aim to investigate chromatin-associated functions of lncRNAs that were recently discovered in the lab, to assess their role in the modulation of cancer cell identity and, importantly, their impact to intratumoral heterogeneity.

Three key questions will be addressed in this study: 1) whether newly discovered lncRNAs are involved in modulation of cancer cell properties, in which cellular compartment and with which protein partners? 2) What are the epigenetic mechanisms underlying lncRNA-mediated control of cellular identity during EMT? 3) What are the chromatin and lncRNA signatures of prostate tumors at single-cell resolution? And whether they define distinct cellular subpopulations and allow clonal tumor dissection due to high intratumoral heterogeneity?

Together, obtained results will bring insights into the lncRNA function in a control of cellular identity underlying intratumoral heterogeneity and distinct clinical outcomes of cancer progression.

International, interdisciplinary & intersectoral aspects of the project

This project appeals to interdisciplinary approaches at the forefront of RNA and molecular oncology studies including RNA imaging and high throughput sequencing techniques in bulk and single-cell levels. The PhD student will develop and apply specific skills in all aforementioned fields in the frame of institutional and international collaborations.

He/she will tightly interact with Dr. N. Sanjana (NYU/NYGC, USA) for the CRISPR screen of functional lncRNA, with Dr. E. Bertrand (IGMM, Montpellier) for single-molecule RNA imaging, with Dr. C. Vallot (IC) and HiFiBiO (Paris) for microfluidic based RNA and chromatin profiling, with medical experts who will provide us with primary prostate tumor samples, and finally, with bioinformaticians for RNA/ChIP-seq data analysis.

Recent publications

1. **M. Pinskaya**, Z. Saci, M. Gallopin, N. H. Nguyen, V. Firlej, M. Gabriel, M. Descrimes, A. de la Taille, A. Londoño-Vallejo, Y. Allory, D. Gautheret, **A. Morillon**. Alignment-free discovery workflow identifies RNA signature of prostate cancer. Science Trans Med (submitted).

2. Wery M, Gautier C, Descrimes M, Yoda M, Migeot V, Hermand D, **Morillon A** (2018) Bases of antisense lncRNA-associated regulation of gene expression in fission yeast. PLoS Genet. 2018 Jul 5; 14(7):e1007465.

3. Meseure D, Vacher S, Lallemand F, Alsibai KD, Hatem R, Chemlali W, Nicolas A, De Koning L, Pasmant E, Callens C, Lidereau R, **Morillon A**, Bieche I (2016) Prognostic value of a newly identified MALAT1 alternatively spliced transcript in breast cancer. Br J Cancer. Jun 14; 114(12).

4. Jarroux J, **Morillon A**, **Pinskaya M**. (2018) History, Discovery, and Classification of lncRNAs. Adv Exp Med Biol. 2017;1008:1-46 (review)

Expected profile of the candidate

Highly motivated students interested in regulatory noncoding RNAs and molecular basis of cancer are encouraged to apply. Candidates should show solid capacity for independent and creative thinking and have a strong background in RNA biology, cell biology, genetics, and gene expression regulation bases in eukaryotes. Laboratory skills in cell culture, basic RNA protocols, CRISPR tools are essential. Some expertise or notion of high throughput sequencing, RNA imaging approaches, and bioinformatics is a plus but not compulsory.