2017-12

IC-**3i** International PhD Program

PhD thesis project

2018 Call for application

Modeling the dynamics and heterogeneity of epigenetic and transcriptomic states during treatment and acquisition of resistance in breast cancer

General information

Call	2018
Reference	2017-12-VALLOT
Keyword(s)	Bioinformatics, Epigenomics, Transcriptomics, Single-cell, Breast cancer

Director(s) and team

Thesis director(s)	Celine Vallot
Research team	Dynamics of epigenetic plasticity in cancer
Research department	UMR3244 – Dynamics of Genetic Information

Description of the PhD thesis project

The DEpiC group (Dynamics of epigenetic plasticity in cancer) is a newly created research group at Institut Curie (Paris) with extensive expertise in multi-omics analysis and epigenetics. We benefit from a unique access to clinical databases and sample collections, as well as top-of-the line technological facilities including a next generation sequencing platform and cluster computing facilities. The group is interested in the dynamics of acquisition of epigenetic alterations in breast cancer. The epigenome is massively remodeled through the redistribution of epigenetic modifications in cancer, which can lead to the aberrant silencing or activation of gene expression. Considering their dynamic nature, such epigenetic and transcriptional plasticity could largely participate to resistance phenomena in tumors. Understanding the dynamics of these epigenetic remodeling events will be decisive to grasp their potential as therapeutic targets to enhance or restore sensitivity to treatment.

This PhD project aims for an integrated molecular, epigenomic & transcriptomic, characterization of breast cancer to model resistance to therapy. Thanks to a unique collection of patient-derived xenograft samples and combination of datasets, incorporating both transcriptomic and epigenomic single-cell sequencing data, we will address the complexity and dynamics of epigenetic traits during in vivo treatment with chemotherapy and with the appearance of resistant phenomena. We propose to develop and apply novel statistical modeling approaches to identify epigenetic features specific of resistant cells. In particular, our project will tackle for the first time the heterogeneity of chromatin states within tumors and its evolution during treatment. Altogether, by modeling the dynamics of epigenetic states in a population of tumor cells under treatment, we wish to identify epigenetic events potentially driving resistance and delineate the typical epi-transcriptomic profiles of resistant cells.

International, interdisciplinary & intersectoral aspects of the project

This PhD project stands at the crossroads of several disciplines; not only does it rely on extensive bioinformatics and statistical analyses, but also on cutting-edge molecular biology experiments (single-cell omics approaches), and on translational research grounds with the use of unique PDX models.

To support our analyses, we are developing a collaboration with the Satijab lab in New York Genome Center at NYU, a bioinformatics group with an extensive expertise in scRNAseq analysis. We have also set up a collaboration with the company HiFiBio to generate unique single-cell datasets for chromatin-immunoprecipitation experiments.

Recent publications

1. **Vallot C**, Patrat C, Huret C, Collier A, Casanova M, Liyakat Ali T, Tosolini M, Heard E, Rugg-Gunn P, Rougeulle C.
XACT noncoding RNA competes with XIST in the control of X chromosome activity during human early development.
Cell Stem Cell. 2017, 20(1):102-111

2. **Vallot C**, Ouimette J*, Makhlouf M, Féraud O, Pontis J, Côme J, Martinat C, Bennaceur-Griscelli A, Lalande M, Rougeulle C.
Erosion of X chromosome inactivation in human pluripotent cells initiates with XACT coating and depends on a specific heterochromatin landscape.
Cell Stem Cell. 2015, 16(5):533-46

3. Lazorthes S, **Vallot C**, Briois S, Aguirrebengoa M, Thuret JY, St Laurent G, Rougeulle C, Kapranov P, Mann C, Trouche D, Nicolas E.
A vlincRNA participates in senescence maintenance by relieving H2AZ-mediated repression at the INK4 locus.
Nat Commun. 2015, Jan 20;6:5971

4. **Vallot C**, Herault A, Boyle S, Bickmore WA, Radvanyi F.
PRC2-independent chromatin compaction and transcriptional repression in cancer.
Oncogene. 2015, 34(6):741-51

5. **Vallot C**, Huret C, Lesecque Y, Resch A, Oudrhiri N, Bennaceur-Griselli, Duret L, Rougeulle C.
XACT, a long non-coding transcript coating the active X chromosome in human pluripotent cells.
Nat. Genet. 2013, 45(3):239-41

Expected profile of the candidate

We are looking for applicants with a strong background in bioinformatics and statistics and a high capacity for independent and creative thinking. Experience with the analysis of NGS omics datasets and advanced usage of the R language are strongly recommended. Background in cancer biology and/or epigenetics is a plus but not compulsory. The project highly relies on the mining of single-cell omics datasets, for which the applicant should have either experience or a strong motivation to learn.