Faculté des Sciences
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FORMULAIRE STAGE Recherche-M2 BBSG
(période de stage : du 8 janvier 2017 au 29 juin 2017)

Titre du stage : Implication of alternative promoter usage in normal and leukemic T-cell

Laboratoire (intitulé, adresse, site web) : Theories and Approches of Genomic Complexity - TAGC/Inserm 1090 - Parc Scientifique de Luminy case 928 163, avenue de Luminy 13288 MARSEILLE cedex 09

Equipe : TAGC

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Descriptif du stage :

Since the advent of high-throughput sequencing technologies ten years ago our ability to study the regulatory mechanisms genome wide has profoundly evolved. The development of various methods (e.g. ChIP-seq, RNA-seq, ATAC-seq, MNase-seq...) makes it possible to produce high quality epigenomes that can be used to annotate precisely the human genome in a cell-type dependent manner. This first layer of information is critical to defined both transcribed regions and regulatory regions and is a prerequisite to go further into deciphering the regulatory mechanisms that (i) drive cell fate in physiological conditions (ii) or lead to pathological states including neoplastic disorders. In this regard, our laboratory was a partner of the Blueprint European Project aimed at producing epigenomes for a large panel of hematopoietic cells. In collaboration with the Necker Hospital, TAGC has produced epigenomes for developing T-cells and T cell lymphoblastic leukemia (T-ALL).
The combination of ChIP-seq and RNA-Seq technology provides a very powerful way to study the control of alternative splicing mechanisms. One particular event is the use of alternative 5' exon (A5E) that results from alternative promoter usage and may leads to RNA and proteins with alternative or altered functions. Although, A5E usage is a rather common phenomenon, but its underlying molecular mechanisms and its role in pathogenicity are poorly understood. The first objectives of this Master II project will thus be (i) to setup a method to search for A5E events by combining RNA-Seq/ChIP-seq data, (ii) to create a catalog of A5E occurrences across normal T-cell development and T-ALL, (iii) to define a set of genes whose promoter usage vary between normal and pathological conditions (iv) to assess the impact of A5E on proteins. In order to understand the mechanisms driving this perturbation we will then focus on the exhaustive characterization of the promoters and transcripts at the genome level, epigenome level, interactome level (bound transcription factors) and variation level (CNV, mutation...). This last step should help us to emphasize some of the molecular events that control A5E usage in physiological conditions. This approach is also expected to provide clues into the molecular events driving T cell leukemia. According to the stage of completion some experiments at the bench could be envisioned to validate isoforms and to go further in the dissection of this biological mechanism (e.g. CRISP/Cas9).

We are looking for a motivated and enthusiastic candidate. She/He will benefit from working within a dynamic and multidisciplinary group, in close collaboration with the TGML (Transcriptomique et Génomique de Marseille-Luminy) sequencing facility, using state of the art genomic and bioinformatic approaches. Some knowledge of bash and Python and/or R languages is required. Knowledge of a scientific workflow management system (e.g snakemake, nextflow, galaxy…) would be an asset. However, the successful candidate may also expect to reinforce his/her technical skills through in-house training.