INSERM U1163 Unit
Imagine Institute

Postdoctoral position in statistical learning for biology

Context

Imagine is an interdisciplinary research center focused in human genetic diseases with the ultimate goal of improving clinical care through the provision of new diagnostic tools and new therapeutic solutions. Imagine is affiliated with the Université Paris Descartes (Sorbonne Paris Cité), the INSERM French National Institute for Medical Research and the Paris Public Hospitals Group (Assistance Publique-Hôpitaux de Paris). The Institute is currently composed of 25 labs and 3 associated labs in various fields including genetics, immunology, infectious diseases, hematology, clinical bioinformatics...

The project is conducted at the interface of the human lymphohematopoiesis laboratory (*Imagine* Institute) headed by M Cavazzana and I André-Schmutz and the cell and gene therapy laboratories (Necker's hospital) headed by M Cavazzana. This is an interdisciplinary project at the interface between clinic, biology and statistical modeling which is conducted by E Six a senior research fellow, in close collaboration with A Guilloux, professor at the Laboratory of Mathematics and Modeling (Genome and Statistics team, LaMME, UEVE - Paris Saclay, France).

Gene therapy by ex vivo transduction of haematopoietic stem and progenitor cells (HSPCs) harvested from diseased individual is more and more used as treatment for severe, cell-intrinsic, inherited defects of the lymphohaematopoietic system (primary immune deficiencies, hemoglobinopathies). The therapeutic vector (retrovirus) integrates into the genome at unique position in each hematopoietic stem and progenitors cell, subsequently transmitted to all its progeny i.e. all circulating blood cells. The analysis of integration sites (IS) thus allows to understand the hierarchy of human haematopoiesis and the impact of the disease on haematopoiesis. Beside fundamental discoveries, the knowledge generated by these studies will help us to actively implement new treatment protocols.

Project description

Several studies have highlighted murine hematopoietic stem cell (HSC) heterogeneity using single cell transplantation, clonal tracking barcoding analysis as well as RNAseq single cell analysis. We propose to develop new approaches to decipher the hematopoietic hierarchy in the human system and explore the dynamic of the thymus. The follow-up of gene therapy trials give us the unique opportunity to track progenitor cells and their descendants through deep sequencing analysis of retroviral integration sites (IS) through LM-PCR and Illumina sequencing using a new INSPIIRED pipeline (collaboration with F Bushman, University of Pennsylvania, Philadelphia, USA). In the context of human gene therapy trials conducted in Necker biotherapy department for Wiskott–Aldrich syndrome, beta-hemoglobinopathies and for X-linked severe combined immune deficiency, we have already isolated and identify more than 100 000 retroviral integration sites (IS) in the genome of circulating blood cells.

In initial analysis, using clustering algorithms (Kmeans and Latent Dirichlet Allocation, LDA), we identified different groups of IS clones corresponding to different

human hematopoietic differentiation programs with different levels of contribution to the myeloid and lymphoid lineages.

The aim of the project is to develop models and associated statistical methods and algorithms to further understand human hematopoietic differentiation programs and hierarchy, and to dissect human T cell dynamic

Expected skills

The ideal candidate would combine
- A PhD in statistics or biostatistics or bioinformatics
- Good programming skills (R, Python).
- Strong knowledge of statistical learning
- Prior experience in statistical modeling
- Interest/skills in biological data analysis

We offer

1 year renewable contract opened from September 2017
Salary depending on experiences
http://www.institutimagine.org/fr/recrutement.html

How to apply

Interested candidates should submit a motivation letter, detailed CV and names /e-mail addresses of two referent persons to Dr. Sarah Enouz (sarah.enouz@institutimagine.org).

Selected publications

1. Berry B*, Nobles C*, Six E*, Wu Y*, Malani N*, Sherman E*, Dryga A*, Everett J, Male F, Bailey A, Bittinger K, Drake MJ, Caccavelli L, Bates P, Hacein-Bey-Abina S, Cavazzana M, and Bushman FD. INSPIIRED: quantification and visualization tools for analyzing integration site distributions. **Mol Ther Meth Clin Dev. In press.**
2. Sherman E*, Nobles C*, Berry B*, Six E*, Wu Y*, Dryga A*, Malani N, Male F, Reddy S, Bailey A, Bittinger K, Everett J, Caccavelli L, Drake MJ, Bates P, Hacein-Bey-Abina S, Cavazzana M, and Bushman FD. INSPIIRED: a pipeline for quantitative analysis of sites of new DNA integration in cellular genomes. **Mol Ther Meth Clin Dev. In press.**
3. Cavazzana C, Six E, Lagresle-Peyrou C, André-Schmutz I, Hacein-Bey-Abina S. Gene therapy for SCID-X1 : Where do we stand ? **Human Gene Therapy. 2016** Feb;27(2):108-16.
4. Hacein-Bey Abina S, Gaspar BH, Blondeau J, Caccavelli L, Charrier S, Buckland K, Picard, C, Six E, Himoudi N, Gilmour K, McNicol A, Hara H, Xu-Bayford J, Rivat R, Touzot F, Mavilio F, Lim A, Treluyer J, Héritier S, Lefrere F, Magalon J, Pengue-Koyi I, Honnet G, Blanche S, Sherman EA, Male F, Berry C, Malani N, Bushman FD , Fischer A, Thrasher A, Galy A, Cavazzana M. Clinical benefit of Gene Therapy in Severe Wiskott-Aldrich Syndrome Patients. **JAMA. 2015.** 313(15):1550-63.
5. Hacein-Bey-Abina S, Pai SY, Gaspar HB, Armant M, Berry CC, Blanche S, Bleesing J, Blondeau J, de Boer H, Buckland KF, Caccavelli L, Cros G, De Oliveira S, Fernández KS, Guo D, Harris CE, Hopkins G, Lehmann LE, Lim A, London WB, van der Loo JC, Malani N, Male F, Malik P, Marinovic MA, McNicol AM, Moshous D, Neven B, Oleastro M, Picard C, Ritz J, Rivat C, Schambach A, Shaw KL, Sherman EA, Silberstein LE, Six E, Touzot F, Tsytsykova A, Xu-Bayford J, Baum C, Bushman FD, Fischer A, Kohn DB, Filipovich AH, Notarangelo LD, Cavazzana M, Williams DA, Thrasher AJ. A modified γ-retrovirus vector for X-linked severe combined immunodeficiency. **N Engl J Med. 2014**; 371(15):1407-17.