COLLEGE ED BIOLOGIE DOCTORAL SANTE PAYS DE LA LOIRE

Year 2023/2024

THESIS TOPIC

Subject N° (to be completed by the ED):	**FUNDING:** ☒ **Requested** ☐ **Acquired**	**Funding origin:**
Thesis title: **Description of epigenetic biomarkers and molecular interaction networks involved in chronic kidney allograft rejection** *(Description des biomarqueurs épigénétiques et réseaux d'interactions moléculaires impliqués dans le rejet chronique en transplantation rénale)*		3 keywords: DNA methylation Kidney transplantation Multi-omics
Unit / team: **UMR1064 CR2TI / iTHINK team 3**		
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Socio-economic and scientific context (approximately 10 lines):

Kidney transplantation is the best therapeutic strategy for end-stage kidney disease, a growing public health issue. Long-term graft survival remains insufficient and chronic humoral rejection is considered the main cause of graft loss. The underlying molecular factors are largely unknown beyond the role of HLA and the therapeutic options remain limited. Understanding the non-HLA pathophysiological mechanisms involved in chronic humoral rejection is therefore a major challenge for preventing this type of events and improving the management of kidney transplanted patients. Blood omics represents a promising alternative to biopsy for deciphering the molecular bases of long-term graft survival and identifying minimally invasive biomarkers. Few reports focusing on one single omics (*e.g.* genomics or transcriptomics) have been published so far, but the sample size remained limited and the clinical phenotypes were heterogeneous.

Working hypothesis and aims (approximately 8 lines):

We hypothesize that implementing a multi-layer functional genomics analysis combining genomics, transcriptomics and epigenomics in a large, monocentric and well-defined clinical cohort of kidney transplanted patients will contribute to unlocking the challenge of long-term kidney allograft survival. This PhD project aims to (1) identifying DNA methylation epigenetic sites, and (2) methylome-genome molecular interaction networks associated with chronic kidney allograft humoral rejection.

- GWAS data are available for 1978 donor-recipient pairs
- Transcriptomic (RNAseq and miRNAseq) data are available for 167 PBMCs (subgroup of the GWAS cohort)
- DNA methylation epigenomic data under generation for 167 PBMCs

The ambition of the project is to run the first extensive DNA methylation screening of chronic humoral rejection in kidney transplantation in order to better understand the pathophysiology, to identify potential therapeutic targets, and to define potential minimally invasive biomarkers predicting post-transplantation events.

Main milestones of the thesis (approximately 12 lines):

- Quality controls and primary analysis of DNA methylation data
- **E**pigenome-**W**ide **A**ssociation **S**tudy (EWAS) to identify differentially methylated positions during chronic humoral rejection
- **E**pigenome-**W**ide **A**ssociation **S**tudy (EWAS) to identify differentially methylated regions during chronic humoral rejection
- Definition of molecular interaction networks by combining genomic and DNA methylation epigenomic datasets (meQTLs)
- TWAS-like strategy (**T**ranscriptome-**W**ide **A**ssociation **S**tudy) to integrate with a machine-learning algorithm genomic and meQTL data to identify gene expression regulatory factors involved in chronic humoral rejection
- Writing scientific communications
- Developing a biomedical collaboration network (including through conferences)
- PhD thesis manuscript writing

Scientific and technical skills required by the candidate (2 lines):

Genomics, bioinformatics, data science and biostatistics
Interdisciplinarity, independence, scientific curiosity

3 publications from the team related to the topic (last 5 years):

1. Ba R, Durand A, Mauduit V, Chauveau C, Le Bas-Bernardet S, Salle S, Guérif P, Morin M, Petit C, Douillard V, Rousseau O, Blancho G, Kerleau C, Vince N, Giral M, Gourraud PA, Limou S. KiT-GENIE, the French genetic biobank of kidney transplantation. EJHG, 2023; 31(11):1291-1299.

2. Ba R, Geffard E, Douillard V, Simon F, Mesnard L, Vince N, Gourraud PA, Limou S. Surfing the big data wave: omics data challenges in transplantation. Transplantation, 2022;106(2):e114-e125.

3. Dubois F, Limou S, Chesneau M, Degauque N, Brouard S, Danger R. Transcriptional meta-analysis of regulatory B cells. Eur J Immunol, 2020; 50(11):1757-1769.

National and international collaborations:

- Nephrology department of Nantes Hospital
- DIVAT cohort
- iGeneTRAiN consortium