Proposition de sujet de thèse CNRS-L/UPD

2017-2018

II.Fiche de Renseignements sur le laboratoire d'accueil au Liban

Université ou centre de recherche : Lebanese American University

Laboratoire d'accueil : Gilbert and Rose-Marie Chagoury school of medicine

Nom du Directeur du laboratoire : Dr Pierre Zalloua

Adresse : Byblos Main campus, block A

Ville : Byblos

Tél./Fax/Mél : 09547254, ext:2855 ; pierre.zalloua@lau.edu.lb

Faculté ou organisme auquel est affilié le laboratoire d'accueil : Human Genetics

Nom du Directeur de thèse : Dr Pierre Zalloua

Le Directeur de thèse fait-il partie du laboratoire d'accueil : Oui

Si non, précisez son rattachement et ses coordonnées :

- Principaux thèmes de recherche de l'équipe où sera effectué le travail de thèse :

Molecular anomalies in people with Type 1 diabetes and coronary artery disease (CAD): Identification of susceptibility genes for complex diseases (Type 1 Diabetes, cardiovascular disease and cancer) and their interaction with the environment. Correlation of gene x environment interactions with disease onset and progression.

Genetic links between various Middle Eastern and Mediterranean populations: Work in the field of population patterns of human migrations using DNA in order to study their genetic commonalities.

- Liste des publications récentes de l'équipe (pertinentes au sujet proposé) :

Platt DE, Ghassibe Sabbagh M, Salameh P, Salloum AK, Haber M, Mouzaya F, Gauguier D, Al-Sarraj Y, El-Shanti H**, Zalloua PA**, Abchee AB. Caffeine impact on metabolic syndrome components is modulated by a CYP1A2 variant. ***Ann Nutr Metab*** 68(1):1-11 (2016)

Hedjazi L, Gauguier D, **Zalloua P**, Nicholson JK, Dumas ME, Cazier JB. mQTL.NMR: An integrated suite for genetic mapping of quantitative variations of 1H NMR-based metabolic profiles. ***Anal Chem*** 87:4377-84 (2015)

Merhi M, Demirdjian S, Hariri E, Sabbah N, Youhanna S, Ghassibe-Sabbagh M, Naoum J, Haber M, Othman R, Kibbani S, Chammas E, Kanbar R, Bayeh HE, Chami Y, Abchee A, Platt DE, **Zalloua PA**, Khazen G. Impact of inflammation, gene variants, and cigarette smoking on coronary artery disease risk. ***Inflamm Res*** 64(6):415-22 (2015)

Milane A, Khazen G, Zeineddine N, Amro M, Masri L, Ghassibe-Sabbagh M, Youhanna S, Salloum AK, Haber M, Platt DE, Cazier JB, Othman R, Kabbani S, Sbeite H, Chami Y, Chammas E, El Bayeh H, Gauguier D, Abchee AB, **Zalloua PA**, Barbari A. "Association of coronary artery disease and chronic kidney disease in Lebanese population." ***Int J Clin Exp Med*** 8(9):15866-77 (2015)

Ghassibe-Sabbagh M, Deeb M, Salloum AK, Mouzaya F, Haber M, Al-Sarraj Y, Chami Y, Akle Y, Hirbli K, Nemr R, Ahdab R, Platt DE, Abchee AB, El-Shanti H, **Zalloua PA**. Multivariate epidemiologic analysis of type 2 diabetes mellitus risks in the Lebanese population. ***Diabetol Metab Synd*** 6(1):89 (2014)

Milane A, Abdallah J, Kanbar R, Khazen G, Ghassibe-Sabbagh M, Salloum AK, Youhanna S, Saad A, El Bayeh H, Chammas E, Platt DE, Hager J, Gauguier D, **Zalloua P**, Abchee A, and FGENTCARD Consortium. Association of hypertension with coronary artery disease onset in the Lebanese population. ***Springerplus*** 2193-1801-3-533 (2014)

The CARDIoGRAMplusC4D Consortium. Large-scale association analysis identifies new risk loci for coronary artery disease. ***Nature Genetics*** 45(1):25-33 (2013)

Haber M, Gauguier D, Youhanna S, Patterson N, Moorjani P, Botigué LR, Platt DE, Matisoo-Smith E, Soria-Hernanz DF, Wells RS, Bertranpetit J, Tyler-Smith C, Comas D, **Zalloua PA**. Genome-wide diversity in the Levant reveals recent structuring by culture. ***PLoS Genet*** 9(2):e1003316 (2013)

Ghassibe-Sabbagh M, Platt DE, Youhanna S, Abchee AB, Stewart K, Badro DA, Haber M, Salloum AK, Douaihy B, el Bayeh H, Othman R, Shasha N, Kibbani S, Chammas E, Milane A, Nemr R, Kamatani Y, Hager J, Cazier JB, Gauguier D, **Zalloua PA**, and FGENTCARD Consortium. Genetic and environmental influences on total plasma homocysteine and its role in coronary artery disease risk. ***Atherosclerosis*** 222:180-6 (2012)

Hager J, Kamatani Y, Cazier JB, Youhanna S, Ghassive-Sabbagh M, Platt DE, Abchee AB, Romanos J, Khazen G, Othman R, Badro DA, Haber M, Salloum AK, Douaihy B, Shasha N, Kabbani S, Sbeite H, Chammas E, El Bayeh H, Rousseau F, Zelenika D, Gut I, Lathrop M, Farrall M, Gauguier D, **Zalloua PA**. Genome-wide association study in a Lebanese cohort confirms PHACTR1 as a major determinant of coronary artery stenosis. ***PLoS ONE*** 7(6):e38663 (2012)

Saade S, Cazier JB, Ghassibe-Sabbagh M, Youhanna S, Badro DA, Kamatani Y, Hager J, Yeretzian JS, El-Khazen G, Haber M, Salloum AK, Douaihy B, Othman R, Shasha N, Kabbani S, Bayeh HE, Chammas E, Farrall

M, Gauguier D, Platt DE, **Zalloua PA**. "Large scale association analysis identifies three susceptibility loci for coronary artery disease." ***PLoS One*** 6(12):e29427 (2011)

La thèse sera-t-elle effectuée en co-tutelleou co-direction:

III. Fiche de Renseignements sur le laboratoire d'accueil à l'UPD

Laboratoire d'accueil : INSERM UMRS1138

Nom du Directeur du laboratoire : Dr Dominique Gauguier

Adresse : University Paris Descartes, Sorbonne Paris Cité, INSERM UMR_S 1138, Cordeliers Research Centre, 15 rue de l'Ecole de Médecine

Code postale-Ville : 75006 Paris, France

Tél./Fax/Mél : +33 144277156

Ecole doctorale auquel est affilié le laboratoire d'accueil : MTCI

Nom du Directeur de thèse : Dr Dominique Gauguier

Le Directeur de thèse fait-il partie du laboratoire d'accueil : Oui

Si non, précisez son rattachement et ses coordonnées :

- Principaux thèmes de recherche de l'équipe où sera effectué le travail de thèse :

Analysis of pathophysiological and molecular mechanisms associated with epigenetic regulations and gene x environment interactions underlying human multifactorial disorders through investigations in rodent models and translational studies in humans

Characterization of the biological function of genes and metabolite biomarkers associated with common diseases at the organ and cellular levels.

- Liste des publications récentes de l'équipe (pertinentes au sujet proposé) :

Dumas ME, Domange C, Calderari S, Rodríguez Martínez A, Ayala R, Wilder SP, Suarez Zamorano N, Collins SC, Wallis RH, Gu Q, Wang Y, Hue C, Otto GW, Argoud K, Navratil V, Mitchell SC, Lindon JC, Holmes E, Cazier JB, Nicholson JK, **Gauguier D**. Topological analysis of metabolic networks integrating co-segregating transcriptomes and metabolomes in type 2 diabetic rat congenic series. ***Genome Med*** 8(1):101 (2016)

Kaisaki PJ, Otto GW, Argoud K, Collins SC, Wallis RH, Wilder SP, Hue C, Calderari S, Bihoreau MT, Cazier JB, Mott R, **Gauguier D**. Transcriptome profiling in rat inbred strains and experimental cross reveals discrepant genetic architecture of genome-wide gene expression. ***Genes, Genomes, Genetics*** 6:3671-3683 (2016)

Platt DE, Ghassibe Sabbagh M, Salameh P, Salloum AK, Haber M, Mouzaya F, **Gauguier D**, Al-Sarraj Y, El-Shanti H, Zalloua PA, Abchee AB. Caffeine impact on metabolic syndrome components is modulated by a CYP1A2 variant. ***Ann Nutr Metab*** 68(1):1-11 (2016)

CARDIoGRAMplusC4D Consortium. A comprehensive 1000 Genomes-based genome-wide association meta-analysis of coronary artery disease. ***Nature Genetics*** 47(10):1121-30 (2015)

Hedjazi L, **Gauguier D**, Zalloua P, Nicholson JK, Dumas ME, Cazier JB. mQTL.NMR: An integrated suite for genetic mapping of quantitative variations of 1H NMR-based metabolic profiles. ***Anal Chem*** 87(8):4377-84 (2015)

Milane A, Khazen G, Zeineddine N, Amro M, Masri L, Ghassibe-Sabbagh M, Youhanna S, Salloum AK, Haber M, Platt DE, Cazier JB, Othman R, Kabbani S, Sbeite H, Chami Y, Chammas E, El Bayeh H, **Gauguier D**, Abchee AB, Zalloua PA, Barbari A. Association of coronary artery disease and chronic kidney disease in Lebanese population. ***Int J Clin Exp Med*** 8(9):15866-77 (2015)

Milane A, Abdallah J, Kanbar R, Khazen G, Ghassibe-Sabbagh M, Salloum AK, Youhanna S, Saad A, El Bayeh H, Chammas E, Platt DE, Hager J, **Gauguier D**, Zalloua P, Abchee A, and FGENTCARD Consortium. Association of hypertension with coronary artery disease onset in the Lebanese population. ***Springerplus*** 2193-1801-3-533 (2014)

Atanur S, Garcia Diaz A, Maratou K, Sarkis A, Rotival M, Game L, Tschannen MR, Kaisaki PJ, Otto GW, Chun John Ma M, Keane TM, Hummel O, Saar K, Chen W, Guryev V, Gopalakrishnan K, Garrett MR, Joe B, Citterio L, Bianchi G, McBride M, Dominiczak A, Adams DJ, Serikawa T, Flicek P, Cuppen E, Hubner N, Petretto E, **Gauguier D**, Kwitek A, Jacob H, Aitman TJ. Genome sequencing reveals loci under artificial selection that underlie disease phenotypes in the laboratory rat. ***Cell*** 154(3):691-703 (2013)

Rat Genome Sequencing and Mapping Consortium. Combined sequence-based and genetic mapping analysis of complex traits in outbred rats. ***Nature Genetics*** 45(7):767-75 (2013)

The CARDIoGRAMplusC4D Consortium. Large-scale association analysis identifies new risk loci for coronary artery disease. ***Nature Genetics*** 45(1):25-33 (2013)

Haber M, **Gauguier D**, Youhanna S, Patterson N, Moorjani P, Botigué LR, Platt DE, Matisoo-Smith E, Soria-Hernanz DF, Wells RS, Bertranpetit J, Tyler-Smith C, Comas D, Zalloua PA. Genome-wide diversity in the Levant reveals recent structuring by culture. ***PLoS Genet*** 9(2):e1003316 (2013)

Ghassibe-Sabbagh M, Platt DE, Youhanna S, Abchee AB, Stewart K, Badro DA, Haber M, Salloum AK, Douaihy B, el Bayeh H, Othman R, Shasha N, Kibbani S, Chammas E, Milane A, Nemr R, Kamatani Y, Hager J, Cazier JB, **Gauguier D**, Zalloua PA, and FGENTCARD Consortium. Genetic and environmental influences on total plasma homocysteine and its role in coronary artery disease risk. ***Atherosclerosis*** 222(1):180-6 (2012)

Hager J, Kamatani Y, Cazier JB, Youhanna S, Ghassive-Sabbagh M, Platt DE, Abchee AB, Romanos J, Khazen G, Othman R, Badro DA, Haber M, Salloum AK, Douaihy B, Shasha N, Kabbani S, Sbeite H, Chammas E, El Bayeh H, Rousseau F, Zelenika D, Gut I, Lathrop M, Farrall M, **Gauguier D**, Zalloua PA. Genome-wide

association study in a Lebanese cohort confirms PHACTR1 as a major determinant of coronary artery stenosis. ***PLoS ONE*** 7(6):e38663 (2012)

Saade S, Cazier JB, Ghassibe-Sabbagh M, Youhanna S, Badro DA, Kamatani Y, Hager J, Yeretzian JS, El-Khazen G, Haber M, Salloum AK, Douaihy B, Othman R, Shasha N, Kabbani S, Bayeh HE, Chammas E, Farrall M, **Gauguier D**, Platt DE, Zalloua PA. Large scale association analysis identifies three susceptibility loci for coronary artery disease. ***PLoS One*** 6(12):e29427 (2011)

IV. Sujet de thèse

IV.1. Titre

Functional analysis of genetic loci co-associated with metabolomic variables and risk for diabetes and coronary artery disease

*La thèse fait-elle partie d'un projet de recherche financé par le CNRS-L : Non

*La thématique sous laquelle s'inscrit la thèse fait-elle partie des priorités du CNRS-L pour l'année 2017-2018 (voir Annexe) : Oui

- Si oui, précisez (possibilité de choisir plus qu'une) : Cardiovascular diseases

IV.2. Résumé

Healthy aging is one of top priorities in healthcare systems worldwide. It relies on advances in genomics and epidemiology to identify risk loci for common diseases, understand their function and define disease predictive biomarkers. The proposed research aims to analyse metabolomic profiling data in Lebanese patients with diabetes and coronary artery disease (CAD) and map their genetic control through genome wide association with respect to disease risk loci, in order to identify metabolic biomarkers that will be characterized for their function in experimental systems. Disease risk factors and metabolic biomarkers will be related to exposome variables available in the cohort.

The research aims to:

- Document socioeconomic, ethnic, biochemical and lifestyle factors associated with diabetes and CAD in a genetically well-characterized cohort (n>5,000).
- Perform urine metabolomics in a subset of 1,000 patients already used for plasma metabolomics, to identify plasma and urine metabolic patterns that are specific to subsets of diabetic and CAD patients
- Correlate analysis of urine / plasma metabolites with exposome variables and map associated loci in the human genome.

- Establish mechanisms underlying the function of candidate metabolites for CAD and diabetes risk through investigations in experimental systems in vivo and in vitro.

IV.3. Contexte et problématique

According to the International Diabetes Federation (IDF), 32.8 million people or 9.1% of the adult population in the Middle East and North Africa Region had diabetes in 2011. Lebanon is one of the 10 countries with the highest prevalence of diabetes in the world with 7.7%. By 2025, the number of people with diabetes is expected to double in these regions. According to the World Health Organization, the age-standardized mortality rate from cardiovascular disease and diabetes per year was estimated to be 224 in 2008 in Lebanon, which is 1.2 times higher than cancer mortality rate.

The healthcare cost of diabetes and cardiovascular diseases accounts for 2.3% of the total global figure and many governments remain unaware of the current magnitude and future burden of diabetes and CAD in societies. The identification of disease associated molecular markers of diabetes and CAD proposed in the thesis is an area of great unmet needs in Lebanon and in the world. Results will give the potential to reduce the healthcare costs of diabetes and CAD through stricter and earlier management of the disease as well as identifying novel therapeutic targets in a personalized medicine approach.

IV.4. Descriptif des objectifs et de l'impact

The scope of the project is timely as the prevalence of diabetes and CAD keeps progressing with ever increasing lifespan in our societies. Its specific objectives are to:

1) Identify the socioeconomic, ethnic, biochemical and lifestyle factors associated with diabetes and CAD in Lebanon in a genetically well-characterized cohort (n>5,000).
2) Acquire urine NMR metabolomic profiles in a subset of 1,000 patients already used for plasma metabolomic profiling, in order to correlate plasma and urine metabolic patterns and test correlations with diabetes and CAD, as well as with exposome data.
3) Localise in the genome genes that regulate metabolomic variables and test their co-localisation with risk loci for diabetes and CAD already identified in the cohort through genome wide association.
4) Characterize the associations between genetic variants and composite phenotype patterns to establish biological pathways underlying the function of candidates, which will be validated in experimental systems in vivo and in vitro.

The project will deliver novel information on genetic risk factors for diabetes and CAD in the Lebanese population, as well as relationships with exposome variables. We anticipate that results from this research will provide healthcare advances and progress in disease therapeutics and prognostics in Lebanon.

IV.5. Aspect appliqué et/ou aspect innovateur

The project will provide advances in our knowledge of the pathological pathways and genetic and non-genetic factors involved in diabetes and CAD in the Lebanese population. It participates in worldwide efforts to identify disease genetic risks, as illustrated by the integration of genomic data in the cohort used in the project in multiple international meta-analyses. We will integrate urine and plasma metabolomic data with biological and clinical information available in the cohort, and use these molecular phenotypes to enhance disease endophenotype data in the patients and define risk loci underlying diabetes and CAD biomarkers. We will be able to assess the different genetic and environmental determinants of CAD in elderly diabetics, in addition to studying age-related markers and markers associated with specific ethnic or racial groups. Moreover, an interesting aspect of this field that is yet to be fully investigated is the role of gene-gene and gene-environmental effects on the risk of CAD in diabetes. Beyond the innovative aspects of defining metabolomic-based metabolic biomarkers that will be applied in genome-wide association studies, the project may have important outcomes in patients' healthcare with the implementation of personalised medicine strategies.

IV.6. Etat des recherches dans le domaine avant la thèse

The project builds on an active collaboration between the laboratories of Dr Pierre Zalloua's at the Lebanese American University and Pr Dominique Gauguier at the Cordeliers research center in Paris, which delivered 17 joint publications since 2011. The theme of the research project, combining genetics and metabolomics to discover metabolite biomarkers associated with diabetes and CAD, is an innovative and promising area of research, which is central in this collaboration between the two groups.

The teams' complementary expertise and their active collaboration maximize the success of the project. The Gauguier team has expertise in molecular genetics, in vivo and in vitro physiology, functional genomics (metabolomics, transcriptomics), statistical genetics and bioinformatics. Dr Pierre Zalloua is a leading authority on the genetics of complex diseases in and among Middle Eastern populations. His research interest is to identify susceptibility genes for complex diseases (Diabetes, cardiovascular disease and cancer), to study their interaction with the environment, and to correlate these interactions with disease onset, manifestation and progression. In the last few years, he has made considerable progress in identifying diabetes and CAD disease susceptibility variants.

IV.7. Programme de recherche prévu pour la thèse et contribution des différents partenaires

During the thesis, genetic and metabolomic approaches will be used to test correlations between metabolites and disease risk and localise loci in the genome associated with urine and plasma

metabolite abundance. In year 1, the focus will be on the identification of the demographic, socioeconomic, ethnic, and biochemical factors associated with diabetes and CAD using well-characterized subjects in our database. Available data derive from primary care clinics serving a wide range of patients. This part of the project will take place in Lebanon (LAU). During the second year, urine metabolome profiling will be carried out in patients followed by correlation between urine and plasma metabolome data and assessment of the contribution of these molecular phenotypes to disease risk. Comparative GWAS analysis of urine and plasma metabolome quantitative data will be carried out in six months under the supervision of Dr Gauguier in Paris. The remainder of Year 2 will be dedicated in Paris to functional analyses of two disease-associated metabolite biomarkers in experimental systems. In the third year, association between genetic variants and composite phenotypic patterns will be carried out to deepen the characterization of biological mechanisms underlying the function of disease risk loci and associated metabolite biomarkers.

Date 24/05/2017

Noms et signatures (directeurs de thèse)

Dominique Gauguier

Pierre Zalloua