PhD Thesis proposal

General Information		
PhD Thesis Title	***Autism spectrum disorders in Lebanese population: detection of specific DNA mutations and identification of metabolic disrupted pathways***	
School	***Faculty of sciences***	
Research Unit	NA	
Laboratory	USEK platform and INSERM France	
Axis	Autism Spectrum Disorders	
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Location (s)	Location 1: USEK	Work shift calendar /per year (40%)
	Location 2: INSERM U1253 - Tours	Work shift calendar /per year (60%)
Funding and scholarship	CNRSL – AUF – USEK (application will be submitted) Or CNRSL – USEK (application will be submitted)	
Applicant Profile and/or Special Requirements		

Subject's national or worldwide Context, Objectives & Research lines (limit : 300 words)
Context
Autism spectrum disorder (ASD) is a developmental disorder that has a complex, heterogeneous and multifactorial etiology, including strong genetic components as well as several environmental and metabolic factors. Indeed, many candidate genes (800 to 1000 genes) have been involved in ASD either by copy number variation (CNV) and/or single nucleotide variation (SNV). Furthermore, using a metabolomics approach on urine of Lebanese ASD children, we have previously shown perturbations in several pathological pathways including amino acids, purine, pyrimidine and oxidative stress pathways. Beside the metabolomics study, studies have shown a dysfunctional folate methionine pathway in many individuals with ASD, a pathway that is very important for DNA synthesis and methylation. It has been shown that MTHFR (Methylenetetrahydrofolate Reductase) gene mutation leads to an increased risk of ASD. This gene mutations limit the conversion of folic acid into activated

folic acid which is essential for growth and development. There are DNA sequence variants associated with the MTHFR gene and the two most investigated are C677T and A1298C as single nucleotide polymorphisms (SNP). In addition, gastrointestinal (GI) symptoms are also shown to be a common comorbidity in ASD. Thus, many studies have revealed modifications in the composition of the fecal flora and metabolites of the gut microbiome in ASD patients. Indeed, several bacterial and fungal gut phyla (eg. Firmicute/ Bacteriodetes) were identified in cohorts of autistic subjects showing the presence of a different microbial community structure. This can support a role for the microbiome as a line between environmental and genetic risk factors that are associated with ASD.

Challenges

Despite the results of several studies conducted on ASD, to date, the exact pathophysiological mechanisms of ASD are still poorly known and there is no biomarker facilitating early diagnosis of ASD to improve patient management and outcomes. The direct genetic causes of ASD are also not yet fully understood and several scientific lacks inhibit the confirmation of any gene directly related to the prognosis of ASD. Moreover, most of the studies on ASD have been conducted in Western populations and rarely in the Eastern area or in the Middle-Eastern / Lebanese areas, and even if studied, its association to MTHFR and the microbiome is not yet fully understood or confirmed.

Objectives

In this study, we aim to:

1. Identify and to assess metabolites in the blood of ASD patients to provide biomarkers for early diagnosis and for a better understanding of the pathophysiology of the disease and to identify the associated metabolic pathways.
2. Identify MTHFR gene polymorphisms in order to understand their impact on the neuronal development and synaptic functions in autistic patients
3. Identify the role of the microbiota in ASD by studying and comparing the fecal ASD patients, siblings and healthy children microbiota.

Research lines

- For metabolomics blood approach, we will use nuclear magnetic resonance and HPLC-MSMS technique to cover a large panel of metabolites.
- For MTHFR mutation we will use the NGS techniques.
- For Microbiota we will use NGS and qPCR techniques.

Outcomes (OCs): What do we wish to achieve?	
OC1:	A better understanding of this multifactorial pathology
OC2:	Early diagnosis based on the identification of biological biomarkers
OC3:	Possible treatment based on the results of MTHFR mutation and microbiota
References (R) (5 most recent peer-reviewed publications)	
R1:	Biomarkers and metabolic disturbances in urines identified by multimodal metabolomics study in Autism Spectrum Disorder in a Lebanese population Bitar Tania, Mavel Sylvie, Emond Patrick, Nadal-Desbarats Lydie, Lefèvre Antoine, Mattar Hanna, Soufia Michel, Blasco Hélène, Vourc'h Patrick, Hleihel Walid & Andres Christian R. Journal of Pharmaceutical and Biomedical Analysis 152 (2018) 57-65 2018
R2:	Developing a skin conductance device for early Autism Spectrum Disorder diagnosis Nehme B., Younes R., Hanna T.A., Hleihel W. and Serhan R.

	Middle East Conference on Biomedical Engineering, MECBMEVolume 2016-November, 15 November 2016, Article number 7745426, Pages 139-142
R3:	Madji Hounoum B, Blasco H, Coque E, Vourc'h P, Emond P, Corcia P, Andres CR, Raoul C, Mavel S (2018). The Metabolic Disturbances of Motoneurons Exposed to Glutamate. In press in Molecular Neurobiology 2018, https://doi.org/10.1007/s12035-018-0945-8.
R4:	Vallée B, Cuberos H, Doudeau M, Godin F, Gosset D, Vourc'h P, Andres CR, Bénédetti H (2018). LIMK2-1, a new isoform of Human-LIMK2, regulates actin cytoskeleton remodeling via a different signaling pathway than its two homologs, LIMK2a/2b. Biochem J. 2018 Oct 29. pii: BCJ20170961. doi: 10.1042/BCJ20170961
R5:	Tastet J, Cuberos H, Vallée B, Toutain A, Raynaud M, Marouillat S, Thépault RA, Laumonnier F, Bonnet-Brilhault F, Vourc'h P, Andres CR, Bénédetti H (2019). LIMK2-1 is a Hominidae-Specific Isoform of LIMK2 Expressed in Central Nervous System and Associated with Intellectual Disability. Neuroscience; 399:199-210.