Proposition de sujet de thèse CNRS-L/UPD

2017-2018

CANA-CNRS pour la recherche marine au Liban

Dans le cadre de l'accord entre le Conseil National de la Recherche Scientifique de la République Libanaise (CNRS-L) et l'Université Paris Descartes (UPD) pour le co-financement des thèses de doctorat dans des thématiques d'intérêt commun, des contrats de recherches doctorales pour l'année 2017-2018 seront mis en place. Ces thèses sont proposées conjointement par un laboratoire de recherche de l'UPD et un laboratoire de recherche libanais dans le cadre d'une convention de co-tutelle ou de co-direction. Ainsi, les équipes souhaitant proposer des thèses de doctorat pour l'année 2016-2017 sont priées de compléter ce formulaire de proposition de sujet de thèse et de l'envoyer par courriel avant le 25 mai 2017 à l'adresse suivante : tamara.elzein@cnrs.edu.lb. Les sujets retenus seront diffusés pour l'appel à candidature et la sélection finale des lauréats se fera par un comité mixte des deux institutions. **Il est à noter que le laboratoire libanais partenaire s'engage à verser durant les 3 ans de thèse 3000 euros par an comme contribution annuelle à la bourse accordée au candidat retenu.**

Pièces à joindre :

- CV du co-directeur libanais
- CV du co-directeur français

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

Université ou centre de recherche : American University of Beirut

Laboratoire d'accueil : Diabetes and Metabolic Disorders

Nom du Directeur du laboratoire : Dr. Assaad A. Eid

Adresse : American University of Beirut, Faculty of Medicine, Department of Anatomy, Cell Biology and Physiological Sciences..

Ville : Beirut Lebanon

Tél./Fax/Mél : +961 1 350 000 ; Ext 4781 – email : ae49@aub.edu.lb

Faculté ou organisme auquel est affilié le laboratoire d'accueil : Faculty of Medicine, Department of Anatomy, Cell Biology and Physiological Sciences

Nom du Directeur de thèse : DR. Assaad A. Eid (HDR)

Le Directeur de thèse fait-il partie du laboratoire d'accueil : **X** Oui / □ Non

Si non, précisez son rattachement et ses coordonnées :

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

  AUB : - Diabetes and Diabetic complications (i.e. peripheral and central nerve damages)
  - Role of ROS in Metabolic Syndromes
  - Novel Therapeutic Drugs for diabets

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

AUB :

1- Eid S, Boutary S, Braych K, Sabra R, Hamdy A, Moodad S, Rashid A, Massaad C, Block K, Gorin Y, Abboud HE, and Eid AA. Rictor/mTORC2 axis Regulates Nox4 Mediated Podocyte Injury in Diabetic Nephropathy. Antioxid Redox Signaling. 25(13):703-719.

2- Eid S, Massaad C, and Eid AA. Oxidative Stress in Diabetic Neuropathy: Strategies for Treatment. Diabetes Case Rep 1:101. doi:10.4172/DCRS.10000101

3- Hichor M, Kumar Sampathkumar N, Montanaro J, Borderie D, Petit PX, Gorgievski V, Tzavara E, Eid AA, Charbonnier F, Grenier J, Massaad C. Paraquat induces peripheral myelin disruption and locomotor defects: crosstalk with LXR and Wnt pathways. Accepted on October 25 in the Antioxid Redox Signaling, December 2016 (Epub ahead of print).

4- MohsenF, Anwar KM, Faraj W, Sauleau AE, Eid AH, and Eid AA. Colorectal Cancer Risk in Diabetes: Double the Trouble in Metabolic diseases. Submitted to JCI March 2017.

La thèse sera-t-elle effectuée en co-tutelle ou co-direction: **co-direction**

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

Laboratoire d'accueil : UMR1124

Nom du Directeur du laboratoire : Dr. Robert Barouki

Adresse : 45 rue des saints-pères

Code postale-Ville : 75006 Paris

Tél./Fax/Mél : 01428621 53 / Frederic.charbonnier@parisdescartes.fr

Ecole doctorale auquel est affilié le laboratoire d'accueil : ED 563 Médicament, Toxicologie, Chimie, Imageries « MTCI ».

Nom du Directeur de thèse : Frédéric Charbonnier

Le Directeur de thèse fait-il partie du laboratoire d'accueil : **X** Oui / □ Non

Si non, précisez son rattachement et ses coordonnées :

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

- Neuromuscular disease (Spinal muscular atrophy and amyotrophic lateral sclerosis
- signalling pathways in neuromuscular disease
- Gene expression regulation and RNA metabolism

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

- Chali F, Desseille C, Houdebine L, Benoit E, Rouquet T, Bariohay B, Lopes P, Branchu J, Della Gaspera B, Pariset C, Chanoine C, Charbonnier F, Biondi O. Long-term exercise-specific neuroprotection in spinal muscular atrophy-like mice. J Physiol. 2016; 594(7):1931-52.
- Biondi O, Branchu J, Ben Salah A, Houdebine L, Bertin L, Chali F, Desseille C, Weill L, Sanchez G, Lancelin C, Aïd S, Lopes P, Pariset C, Lécolle S, Côté J, Holzenberger M, Chanoine C, Massaad C, Charbonnier F. IGF-1R Reduction TriggersNeuroprotective Signaling Pathways in Spinal Muscular Atrophy Mice. J Neurosci. 2015; 35(34):12063-79.
- Branchu J, Biondi O, Chali F, Collin T, Leroy F, Mamchaoui K, Makoukji J, Pariset C, Lopes P, Massaad C, Chanoine C, Charbonnier F. Shift from extracellular signal-regulated kinase to AKT/cAMP response

element-binding protein pathway increases survival-motor-neuron expression in spinal-muscular-atrophy-like mice and patient cells. J Neurosci. 2013; 33(10):4280-94.
- Sanchez G, Dury AY, Murray LM, Biondi O, Tadesse H, El Fatimy R, Kothary R, Charbonnier F, Khandjian EW, Côté J. A novel function for the survival motoneuron protein as a translational regulator. Hum Mol Genet. 2012; 22(4):668-84.
- Biondi O, Lopes P, Desseille C, Branchu J, Chali F, Ben Salah A, Pariset C, Chanoine C, Charbonnier F. Physical exercise reduces cardiac defects in type 2 spinal muscular atrophy-like mice. J Physiol. 2012 Nov 15;590(Pt 22):5907-25.

IV. Sujet de thèse

A faire signer obligatoirement par tous les co-directeurs

IV.1. Study of the crosstalk between NADPH oxydases and Top2a in Spinal Muscular Atrophy.

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

Si oui, précisez :

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

- Si oui, précisez (possibilité de choisir plus qu'une) :
  - Medical sciences: Metabolic Disorders and Neurophysiology and Brain Research
  - Basic science: Molecular & Cellular Biology

IV.2. Résumé (ne pas dépasser 200 mots)

Spinal muscular atrophy (SMA), a fatal neurodegenerative disease with child onsed, caused by a low level of the Survival Motor Neuron (SMN) protein, lead to motorneuron (MN) death and muscular atrophy. Moreover, SMA patients display high blood glucose levels and insulin resistance; two features that can lead can lead to an excess of reactive oxygen species (ROS). ROS plays a central role in several neurodegenerative diseases but their effects in SMA have not been studied yet. Nevertheless. Interestingly, ROS inhibits the correct splicing of *SMN2*. Consequently, understanding the mechanistic pathway involving ROS in SMA is of great importance.

In parallel, we have identified the DNA topoisomerase II alpha (Top2a) as a potential factor involved in SMN2 splicing. Top2a controls DNA topology during replication and transcription but its role in gene expression and RNA splicing regulation is unclear.

The aim of this project is to understand the link between oxidative stress and top2a and to identify the molecular mechanism by which top2a regulate gene expression using as a paradigm SMN gene. In one hand, we will study the crosstalk of oxidative stress and top2a in SMA, in another hand, we will investigate the function of Top2a on SMN2 expression and splicing.

IV.3. Contexte et problématique (ne pas dépasser 200 mots)

SMA, a neurodegenerative disease is caused by *SMN1* gene mutation. The presence of *SMN2* copy gene does not compensate *SMN1* deletion since a polymorphism leads to exon 7 skipping and produces an unstable SMN protein. Thus, the identification of factors that modulate *SMN2* expression and splicing is essential to find potential pharmacological candidates.

ROS production has been identified as a common pathway in several neurodegenerative pathologies, however its role in SMA is not yet defined. We hypothesize that ROS production can contribute to MotorNeuron death in SMA. Moreover, SMA patients showed high levels of blood glucose and were diagnosed with insulin resistance, two conditions associated with increased ROS levels. Interestingly, ROS inhibits the splicing of *SMN2* exon 7. Consequently, understanding the mechanistic pathway involving ROS in SMA is of great importance.

In parallel, we identified Top2a as a potential factor involved in exon 7 splicing. Yet Top2a and ROS crosstalk is not defined. Top2a resolves DNA entanglements that appear during replication and transcription and could be involved in gene expression and RNA splicing.

The aim of this project is to understand the link between oxidative stress and top2a and to identify the molecular mechanism by which top2a regulates gene expression.

IV.4. Descriptif des objectifs et de l'impact (ne pas dépasser 200 mots)

SMA is a devastating and a fatal disease with no effective treatment. Therapeutic solutions are based on understanding the role of SMN in cellular function and identify its cellular and molecular alterations leading to neuronal death. In this project we will focus on the role of Top2a, ROS and its source of production and their crosstalk in inducing SMN alteration. For this we will work on 2 major aims:

1- To study the Gene expression regulation orchestrated by top2a in SMA.The first aim of this project is to decipher the molecular mechanism by which top2a regulate gene expression. Using SMN2 gene model, we will first determine the effect on top2a on SMN2 expression and identify the mechanism involved (Transcription, splicing). Then, we will identify by RNAseq new genes that are also regulated by top2a.
2- To understand the role of NADPH oxidases-induced ROS production in SMN alteration. Also, the crosstalk of NADPH oxidases and Top2a will be studied. Oxidative stress can be initiated by a

number of processes including alteration in the NADPH oxidases that may lead to motor neuron dysfunction through alteration of the SMN pathway.

IV.5. Aspect appliqué et/ou aspect innovateur (ne pas dépasser 200 mots)

SMA Is one of the most common genetic causes of death in children and leads to strong motor disabilities and no cure exists to date. The identification of new factors that could alleviate the symptom of disease is essential.

We have recently identified Top2a as a potential regulator of SMN2 splicing, and we highlighted the role of NADPH oxidases-induced ROS production in neurodegenerative diseases especially neuropathy. Taken together our preliminary data and the aims proposed in this project will bring a new layer in the understanding of the gene regulation role and on the coupling on DNA and RNA metabolisms in SMA. Importantly novel cellular and molecular pathways will be identified and studied to understand the mechanistic alteration in SMA.

Completion of this project will help us understand mechanistic questions that will hopefully provide insight into the best method of therapeutic intervention.

IV.6. Etat des recherches dans le domaine avant la thèse (ne pas dépasser 200 mots)

The laboratory in Beirut defined NADPH oxidase (Noxs) role in inducing neurodegenerative diseases especially diabetic neuropathy. Noxs pathway activation was paralleled by an increase in ROS production and an alteration in the mTOR/p70-S6 kinase pathway from one hand and the mTOR/Akt pathway from the other hand. The role of these alterations in SMA is not studied.

The French group showed that Top2a is underexpressed in spinal cord of SMA mouse model and Akt activation leads to *SMN2* expression augmentation and Top2a expression restoration. While top2a function for DNA topology is known, it is unclear whether top2a regulates specifically gene expression, which genes are regulated and what is the molecular mechanism. Nevertheless, top2a silencing and inhibition influence alternative splicing of several genes and Top2a interacts with splicing factors. Moreover, preliminary results indicate that Top2a overexpression in human SMA fibroblasts improves SMN2 splicing.

We hypothesized that Top2a modulates the splicing either by modifying the transcription velocity or by recruiting splicing factors on *SMN2* gene or pre-mRNAs and that Top2a expression defect can be due to NADPH/mTOR signaling pathway activation.

The expertise and efforts from our 2 laboratories will help achieve the described aims and will set the stage for more future funding.

IV.7. Programme de recherche prévu pour la thèse et contribution des différents partenaires (ne pas dépasser 200 mots)

- **Gene regulation by Top2a** will be performed in the French laboratory: UMRS1124- Eq9, Faculty of Basic and Biomedical Sciences – Paris Descartes University, France.

- **Oxidative stress role in SMA and its crosstalk with Top2a** will be performed in the Lebanese co-director laboratory (Eid's Laboratory, Department of Anatomy, Cell Biology and physiological Sciences, AUB, Beirut, Lebanon).

This study will be divided as follow:

1/ **Analysis of top2a role on *SMN2* expression and splicing.** This will be done by lost and gain of function experiments

2/ **Study of the molecular mechanism behind the SMN alteration.** We will investigate whether Top2a binds directly on SMN2 gene or pre-mRNA and whether top2a acts on transcription or whether it favours spliceosome recruitment by a combination of molecular biology approaches.

3/ **Identification of the set of genes regulated by Top2a by RNA immunoprecipitation sequencing**

4/ Study of Nox role on SMN alteration in SMA. We will assess this by using pharmacological and genetic inhibitors.

5/ **Study the role of NADPH/mTOR/p70 S6 kinase signaling and the role of NADPH/mTOR/Akt signaling in SMA.**

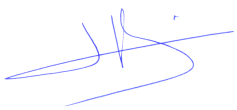
6/ **Crosstalk Identification between Top2a and the different identified signaling pathway described above.**

Both laboratories are committed to the work described in this project.

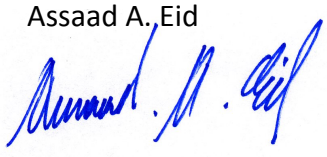
Date 24/05/2017

Noms et signatures (directeurs de thèse)

Frédéric Charbonnier



Assaad A. Eid



Annexe: thématiques prioritaires pour les bourses doctorales 2017-2018

Cultural heritage • Archaeology • Protection, conservation and restoration of artifacts and ancient manuscripts • Archaeometry
Arabic language and History • Arabic linguistics, dynamism, and history • Cognitive linguistics (in Arabic) • History of Science in Arabic civilization • Arabization of softwares
Sociology and political science • Migration sociology • Conflict resolution and Post-conflict societies • Gender and feminist studies • Gender diversity • Ethics in media coverage of conflicts (conventional and social medias)
Business, Economics and Finance • Entrepreneurial University and innovation • Economy of conflict areas • Lebanon as potential destination for offshoring • Actuarial science and Financial risk management • Mathematical and computer modeling applied to finance and economy • Business information decision systems • International finance and emerging markets • Entrepreneurship • Corporate governance • Cross-cultural management • Digital marketing • Internal and external control • Consumer behavior • Enhancing work conditions • Asset pricing, risk management and volatility modeling • Banking policies in the MENA region
Environment, natural resources - Valorization of Lebanese coastal zones - Petroleum studies - Sustainable water management - Renewable energy - Biodiversity and speciation - Mitigation & management of natural risks - Sociology of risk - Air quality - Urban planning in the age of climate change - Environmental law
Agriculture and food - Challenges of agricultural activities

- Food Security
- Food safety & food industry
- Veterinary medicine
- Pest and Alien species

Medical sciences

- Addictive Diseases
- Cancer Research
- Cardiovascular diseases
- Clinical pharmacology. Pharmacy
- Clinical Immunology and Immunopathology
- Clinical Biochemistry
- Clinical Genetics
- Radiotherapy
- Diseases of Bones and Joints
- Endocrinology
- Geriatrics
- Infectious Diseases
- Medical Microbiology
- Mental Disorders, Psychosomatic Diseases
- Metabolic Disorders
- Methods of Epidemiology and Preventive Medicine
- Psychiatry
- Neurophysiology and Brain Research.
- Public Health and Health Services
- Respiratory Diseases
- Ethics in medicine and medical research

Basic science

- Theoretical & Particle physics
- Peaceful use of nuclear energy and technics
- Forensic chemistry
- Green chemistry
- Biomedical engineering
- Molecular & Cellular Biology
- Genetics
- Architecture and Design
- Civil and Environmental Engineering
- Chemical Engineering
- Ergonomy
- Electrical and Computer Engineering
- Industrial Engineering and Management
- Modern Imaging and vision
- Mechanical Engineering