

THESIS TOPIC

Subject N° (to be completed by the ED):	FUNDING: <input checked="" type="checkbox"/> Requested <input type="checkbox"/> Acquired	Funding origin:
<u>Thesis title:</u> How pathological protein aggregates interact with mitochondria in the degenerating neurons of patients affected with Amyotrophic Lateral Sclerosis		<u>3 keywords:</u> - Amyotrophic Lateral Sclerosis (ALS) - Mitochondria - TDP-43
<u>Unit / team:</u> MR CNRS 6015 INSERM U1083 - MITOVASC Physiopathologie cardioVASCuaire et MITOchondriale, équipe Mitolab		
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<u>Socio-economic and scientific context:</u> Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder affecting upper and lower motor neurons in the cortex, brainstem and spinal cord. The disease is responsible for a progressive paralysis leading to death within 2–3 years after the symptoms onset, usually from respiratory failure (Kiernan, 2011 ; Chio, 2013). To date, the only treatment available for ALS is the Riluzole, with a modest efficiency on the progression of the disease. Indeed, most of the clinical trials conducted for the last two decades remained negative, partly due to the lack of knowledge about the pathophysiology of the disease (Mitsumoto, 2014). In recent year, major advances have been made in understanding neurodegeneration in ALS, through the identification of constant post-mortem lesions in degenerating motor neurons, in particular intracytoplasmic inclusions of the protein TDP-43 and mitochondria structural and functional alterations (Neumann, 2006 ; Wang, 2016).		
<u>Working hypothesis and aims:</u> Our research team conducts for more than 15 years projects focusing on mitochondrial alterations in neurodegenerative disorders, using genomics (Bonneau D, 2014 ; Gerber S, 2017 ; Goudenège, 2018), biochemistry (Chevrollier, 2008 ; Guillet, 2010), metabolomics (Chao de la Barca, 2016 ; Bocca et al., 2018) and histological approaches (Chevrollier, 2012 ; Codron, 2018). We recently developed a new super-resolution imaging protocol allowing to perform Stochastic Optical Reconstruction Microscopy (STORM) on post mortem brain samples (Codron et al. in review Nat Comm). This approach allowed us to characterize with unprecedented detail the architecture of intracellular structures in the human brain, opening further gates to a more comprehensive understanding of underlying mechanisms responsible for common neurological diseases. The main objective of this project is to use this innovative technique to characterize with a nanometer-scale precision the intraneuronal lesions observed in ALS, focusing on TDP-43 inclusions and mitochondrial alterations, with the aim of better understanding the pathophysiology and propagation of the disease. With a translational approach, we will attempt to define clinical-pathological correlations and identify endophenotypes among patients, with distinct pathophysiological mechanisms, to contribute to current works on diagnostic and prognostic markers and personalized medicine. Finally, we will focus on similarities and differences between the lesions observed in post-mortem samples and those induced in commonly used cell lines and animal models in the field of ALS research, to identify their strength and limitations.		
<u>Main milestones of the thesis (approximately 12 lines):</u> First Part of the Thesis: using STORM imaging, we will characterize at the nanoscale level the pathological lesions observed in the upper and lower motor neurons of patients affected with ALS, focusing on TDP-43 inclusions and mitochondrial alterations. We will attempt to identify endophenotypes among patients and make assumptions about common and distinct pathophysiological mechanisms in the disease. Second Part of the Thesis: a similar approach will be used to characterize the lesions induced in commonly used cell lines and animal models in the field of ALS research. We will study protein inclusions and mitochondrial alterations in neuronal cell lines stressed by toxic exposure or expressing mutated TDP-43. Thanks to the partnership established two years ago with the Canadian research unit CERVO (Dr Jean-Pierre JULIEN) specialized in the generation of ALS research models, we will also analyze the pathological lesions developed by common (TDP-43A315T, TDP-43G348C) and innovative (TDP-43/UBQLN2, intracerebral injection of TDP-43 aggregates) mice models. Finally, we will study the similarities and differences between these lesions and those observed in post-mortem brain and spinal cord samples of patients affected with ALS to define their strength and limitations. Third part of the Thesis: scientific articles writing, oral communication, and thesis defense.		
<u>Scientific and technical skills required by the candidate:</u> Expertise in Clinical Neuroscience, Histopathology, Cell Imaging (samples preparation, acquisition and image processing), Biostatistics, and scientific writing (English and French).		
<u>3 publications from the team related to the topic (last 5 years):</u> Codron P, Letournel F, Bodin A, Renaud L, Verny C, Duyckaerts C, Julien J-P, Cassereau J, Chevrollier A. Imaging Human Brain at the Nanoscale Level with Stochastic Optical Reconstruction Microscopy (STORM). In review. 2019. Nat Comm. Pozzi S, Thammisetty S, Codron P, Rahimian R, Gravel C, Kriz J and Julien J-P. Single chain antibodies against TDP-43-RRM1 domain as a therapeutic approach for TDP-43 proteinopathy. 2019. Journal of Clinical Investigation. 129 (4), 1581-1595		

Codron P, Cassereau J, Vourc'h P, Veyrat-Durebex C, Blasco H, Kane S, Procaccio V, Letournel F, Verny C, Lenears G, Reynier P, Chevrollier A. Primary fibroblasts derived from sporadic amyotrophic lateral sclerosis patients do not show ALS cytological lesions. 2018. *Amyotroph Lateral Scler Frontotemporal Degener.* 31:1-11

National and international collaborations:

- Dr Franck LETOURNEL : Laboratoire de Neurobiologie et Neuropathologie CHU d'Angers, Angers, France.
- Pr Jean-Pierre JULIEN : CERVO Brain Research Centre, 2601 Chemin de la Canardière, Québec, QC, Canada
- Dr Mathilde DUCHESNE : Laboratoire d'Anatomie Pathologique, Centre Hospitalier Universitaire de Limoges, Limoges, France

Références

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