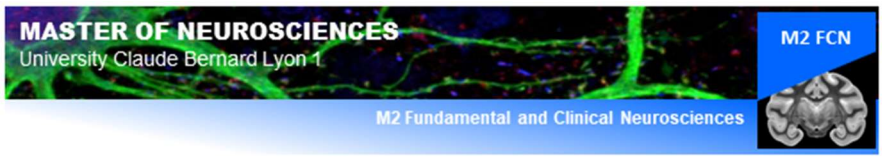

MASTER 2 Fundamental and Clinical Neurosciences

Internship proposal 2026-2027

(internship from January to June 2027)

Host laboratory: *CRNL – Centre de Recherche en Neurosciences de Lyon*

CH Le Vinatier, Bât Neurocampus, 95 Bd Pinel, 69675 Bron cedex

Host team : *TIGER (https://www.crnl.fr/fr/equipe/tiger)*

Internship supervisors : *Stéphane MARINESCO (DR Inserm), Eleni PANAGIOTAKAKI (PH HCL), Baptiste BALANCA (MCU-PH, Lyon 1, HCL)*

Project title : The ATP1A3-deficient rat as an experimental model of alternating hemiplegia of childhood (AHC)

Project summary :

Alternating hemiplegia of childhood (AHC) is a neurodevelopmental disorder characterized by intellectual disability, motor impairments, and paroxysmal episodes such as transient hemiplegia and/or dystonia. Na^+/K^+-ATPase, which plays a crucial role in maintaining ion gradients across the plasma membrane, is implicated in this condition, as the majority of patients have mutations in the *ATP1A3* gene coding for the a3 isoform of the alpha subunit of this ATPase. A decrease in the activity of this pump promotes cortical spreading depolarizations (SDs), waves of near-complete depolarization of neurons and glial cells that propagate across the cortex. Mouse models with mutations in the *ATP1A3* gene show increased susceptibility to SDs. There is a solid theoretical basis for linking paroxysmal hemiplegic/dystonic paroxysmal episodes in patients with AHC to spontaneous SDs caused by a deficiency in the Na^+/K^+-ATPase pump. To better understand the biological mechanisms linking the *ATP1A3* mutation to AHC, mouse models have recently been developed; however, the size of the mouse brain does not allow for continuous monitoring of SDs and cerebral metabolism. We propose to develop a rat model that will allow us to implement intracerebral monitoring techniques during paroxysmal episodes using implantable biosensors. The project will consist of characterizing this rat model carrying the E815K variant of the *ATP1A3* gene. We will assess the animals' general behavior, their locomotor activity, and the presence of paroxysmal plegic and dystonic episodes. In addition, we will record and characterize the presence of SDs in these rats. This new transgenic rat model will thus enable us to determine the mechanism with which the *ATP1A3* gene mutations produce the phenotype of alternating hemiplegia and the role of SDs in this condition.

Methods : behavioral video recordings, electro physiological recordings and signal processing

3-5 recent publications :

1. Chen S, Hexter M, Sabac A, and **Marinesco S** (2026) Brain tissue oxygen pressure monitoring using carbon fiber microelectrodes protected from biofouling by

polyphenylenediamine-polyurethane coating. *Bioelectrochemistry* 171:109281. doi: 10.1016/j.bioelechem.2026.109281

2. Tholance Y, Aboudhiaf S, Balança B, Barcelos GK, Grousson S, Carrillon R, Lieutaud T, Perret-Liaudet A, Dailler F and **Marinesco S.** (2023) Early brain metabolic disturbances associated with delayed cerebral ischemia in patients with severe subarachnoid hemorrhage. *J Cereb Blood Flow Metab* 43 (1) :1967-1982. doi: 10.1177/0271678X231193661
3. S. H.Patel, **E.Panagiotakaki**, B.Liu, et al., "Natural History of Alternating Hemiplegia of Childhood: Vulnerabilities in Early Childhood and Predictive Factors for Long-Term Outcomes," Annals of the Child Neurology Society3 (2025): 260-273, https://doi.org/10.1002/cns3.70037.
4. **Panagiotakaki E**, Tiziano FD, Mikati MA, Vijfhuizen LS, Nicole S, Lesca G, Abiusi E, Novelli A, Di Pietro L; I.B.AHC Consortium; IAHCRC Consortium; Harder AVE, Walley NM, De Grandis E, Poulat AL, Portes VD, Lépine A, Nassogne MC, Arzimanoglou A, Vavassori R, Koenderink J, Thompson CH, George AL Jr, Gurrieri F, van den Maagdenberg AMJM, Heinzen EL. Exome sequencing of ATP1A3-negative cases of alternating hemiplegia of childhood reveals SCN2A as a novel causative gene. Eur J Hum Genet. 2024 Feb;32(2):224-231. doi: 10.1038/s41431-023-01489-4. Epub 2023 Dec 14. PMID: 38097767; PMCID: PMC10853263.
5. Papadopoulou MT, Welniarz Q, Roubertie A, Gras D, Milh M, **Panagiotakaki E**, Roze E. Effect of Oxygen Administration on Paroxysmal Motor Events in Alternating Hemiplegia of Childhood. Mov Disord. 2023 Sep;38(9):1759-1761. doi: 10.1002/mds.29561. Epub 2023 Jul 19. PMID: 37466145.