CSC-RUB PhD Project Proposal

Title: Identifying impaired intrinsic mechanisms underlying decision making and working memory in an episodic ataxia type 2 mouse model.

Sector of research: Neuroscience

Degree awarded: PhD in Neuroscience

Keywords: cerebellum, decision making, working memory, optogenetics, episodic ataxia type 2, synaptic plasticity

Supervisor of PhD project:

Prof. Dr. Melanie D. Mark, Behavioral Neuroscience

Research focus of supervisor:

My research focuses on understanding the mechanisms contributing to the P/Q type calcium channel diseases, episodic ataxia type 2 (EA2) and spinocerebellar ataxia type 6 (SCA6). We created mouse models for EA2 and SCA6 which demonstrate symptoms similar to patients including ataxia, Purkinje cell (PC) degeneration, PC dysfunction, synaptic plasticity impairments and cognitive deficits. During our ongoing research we have gained valuable insights to the mechanisms and functions of the channel in the cerebellum and its role in ataxia, dystonia, absence seizures and cognition. Through the development of GPCR specific optogenetic and chemogenetic tools to control neuronal firing and signaling cascades involved in motor learning and cognition, we are able to dissect the signaling pathways controlling these behaviors which will aid in establishing more effective therapeutic strategies to improve motor learning and cognition in cerebellar degenerative diseases.

Publications: H index of 14 (last 5 yrs); 46 publications

1) Bohne P, ... **Mark MD**. (**2021**) *Hum Mol Genet*. Doi:10.1093/hmg/ddab149.
2) Karapinar R, … **Mark MD***, Siveke I, Herlitze S* (**2021**) *Nature Commun*. 12:4488. *Equal corresponding author.
3) Miao QL, Herlitze S, **Mark MD**, Noebels JL (**2020**) *Brain*. 143(1): 161-174.
4) Eickelbeck D, … **Mark MD**, … Herlitze S (**2019**) *Communications Biology*. 2:60.
5) Maejima T, ... **Mark MD** (**2013**). *J Neurosci.,* **33**(12): 5162-74.

Summary of research plan

Background: Traditionally the cerebellum was thought to be only involved in motor function, but recent evidence demonstrate that it also contributes to cognitive functions through its interconnections with the cortex. Past studies implicate the cerebellum in cognitive functions

such as decision making, working memory and reward-based learning. However, the neural circuitry and intrinsic mechanisms modulating the exchange of information between the cerebellum and cortex are largely unknown. In a recent study we provide evidence that EA2 mice are deficient in their decision making and working memory functions. By implementing our newly designed optogenetic tools which enhance synaptic plasticity and chemogenetics in combination with a reward-based learning task and calcium imaging in PC, we will be able to identify the circuitry and intrinsic mechanisms underlying the cerebellar contribution to decision making and working memory in EA2 mice.

Study objective: To characterize the regions, neurons and type of synaptic plasticity in the cerebellum responsible for the deficits in decision making and working memory in the EA2 mice. Recovery of decision making and working memory impairments in the EA2 mice by manipulating cerebellar neurons with optogenetic and chemogenetic tools.

Expected Results: Lobule VI, Crus I and Crus II of the cerebellum have been previously shown to be involved in decision making and working memory. We will initially investigate the PC activity in these areas from behaving EA2 mice. We anticipate aberrant PC activity and synaptic plasticity in EA2 mice. We also expect to recover this aberrant PC activity with optogenetic or chemogenetic tools. These findings would be new and published.

Methods: The project will apply a multi-disciplinary strategy with established techniques in the lab including neuron specific electrophysiological recordings and calcium imaging combined with optogenetic, chemogenetic and reward based associative learning tasks.

Candidate Requirements: Good English speaking, comprehension and written skills, neuroscience background, mouse handling skills

Motivation for CSC application: My personal motivation to mentor an international student is to foster international scientific exchange of ideas and techniques and to build long lasting collaborations with scientist worldwide who have a common goal to improve the quality of life for individuals suffering from neurodegenerative diseases. Besides the multi-disciplinary state of the art techniques and strategies available, CSC candidate will participate in monthly seminars and meetings focused on the cerebellum with the Department of Prof. Dr. Dagmar-Timmann-Braun at the University of Duisburg-Essen who also works on neurodegenerative diseases in humans, and weekly journal clubs focused on neuroscience with the laboratories of Behavioral Neuroscience and General Zoology and Neurobiology. Moreover, the candidate will be integrated into the Ruhr University Neuroscience Research School and Faculty of Biotechnology and Biology where he or she will have access to international conferences and seminars hosted by various departments and Special Research groups (SFB874 and

SFB1280) on campus. Lastly, being a native English speaker, I will be able to improve the scientific speaking and writing skills of the CSC candidate.