CSC-RUB PhD Project Proposal

Title: Improving motor learning and coordination by sustained training and neuronal stimulation in a spinocerebellar ataxic type 6 mouse model.

Sector of research: Neuroscience

Degree awarded: PhD in Neuroscience

Keywords: cerebellum, ataxia, motor learning, motor coordination, exercise, optogenetics, episodic ataxia type 2, spinocerebellar ataxia type 6

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) Karapinar R, … **Mark MD***, Siveke I, Herlitze S* (**2021**) *Nature Commun*. 12:4488. *Equal corresponding author.
2) Miao QL, Herlitze S, **Mark MD**, Noebels JL (**2020**) *Brain*. 143(1): 161-174.
3) Eickelbeck D, … **Mark MD**, … Herlitze S (**2019**) *Communications Biology*. 2:60.
4) **Mark MD, ...** Herlitze S (**2015**). *J Neurosci.,* **35**(23): 8882-95.
5) Maejima T, ... **Mark MD** (**2013**). *J Neurosci.,* **33**(12): 5162-74.

Summary of research plan

Background: Cerebellar ataxia is a common finding in many neurological disorders, resulting in motor incoordination and a diminished quality of life with no causal treatment. Rehabilitative therapy, particularly physical therapy, is the common treatment. While it does

improve symptoms and delay disease progression, the mechanisms of action remain unclear. The main goal is to identify preserved and compensatory motor learning mechanisms after sustained exercise in the neurodegenerative disease, spinocerebellar ataxia type 6 (SCA6) at different disease stages in mice.

Study objective: To determine if sustained training improves ataxia and motor learning, delays the onset of disease and cerebellar symptoms, reduce the neurodegenerative progression and enhance synaptic plasticity in SCA6 mice. To identify brain regions involved in compensatory learning mechanisms during the progression of the disease using optogenetic manipulations with reach adaptation tasks in SCA6 mice.

Expected Results: Our central hypothesis is that cerebellar malfunctions may initially impact error-based implicit learning, sparing other types of learning such as use-dependent, explicit strategic and reward-based, but as the disease progresses these other forms are also diminished. We anticipate that sustained training will improve motor coordination and learning, synaptic plasticity and neuronal health and delay disease symptom onset. We also expect that use-dependent learning controlled via the motor cortex will compensate for cerebellar error-based learning in the later stages of the SCA6 disease. These findings would be new and published.

Methods: The project will apply a multi-disciplinary strategy with established techniques in the lab including cell specific quantitative real time PCR, neuron specific electrophysiological recordings and calcium imaging combined with optogenetic and behavior approaches such as the reach adaptation task.

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.