TREMENDOS

The role of microglia in the effects of environmental enrichment in neurodegenerative disorders (TREMENDOS)

Environmental enrichment (EE) is an experimental paradigm that combines physical, social, and cognitive stimulation and is associated with beneficial effects in pre-clinical models of several neurodegenerative disorders (NDDs). However, the molecular mechanisms underlying the advantageous effects of EE in NDDs remain largely unclear.

We present here a novel hypothesis that postulates changes in microglial metabolism that affect their phagocytic and inflammatory properties to contribute towards the effects of EE in NDDs. Forming a transnational consortium of scientists with extensive expertise in EE, microglia, and NDDs; we will investigate how individual and combined stimulations in EE affect microglial transcriptomics. We will then investigate the functional response of microglia after EE to pathological aggregates associated with major NDDs, including amyloid, tau and TDP-43. Based on these analyses, we will identify the molecular cascade(s) that enables microglia to efficiently remove pathological aggregates while maintaining a controlled inflammatory response. These identified targets will then be manipulated specifically in microglia in vitro and ex vivo to examine their distinct role in microglial phagocytosis of NDD-associated pathological aggregates. Subsequently, mice with microglia-specific manipulation of the identified target(s) will be crossed with transgenic mouse models of NDDs. This will conclusively establish whether specific microglial pathways underlie the beneficial effects of EE in NDDs. Finally, the results will be corroborated by a human study that will ascertain if specific metabolic signatures are associated with enhanced or reduced microglial phagocytosis of amyloid and healthy synapses.

The results of this study will advance our understanding of the role of microglia in mediating the effects of EE in NDDs and reveal mechanisms via which the efficiency of EE in NDDs could be improved through specific modulation of microglia. This will inform novel therapeutic approaches for several NDDs, including Alzheimer disease.

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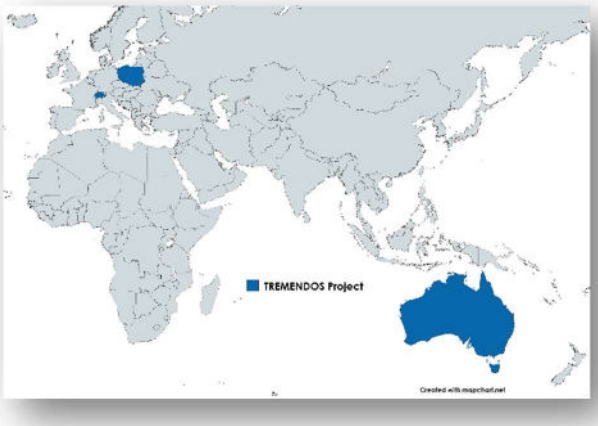
Coordinator : Ali Jawaid
✉ : a.jawaid@nencki.edu.pl



Consortium Members		
	Ali Jawaid	Nencki Institute of Experimental Biology, Poland
	Bozena Kaminska	Nencki Institute of Experimental Biology, Poland
	Rosa Paolicelli	University of Lausanne, Switzerland
	Anthony Hannan	Florey Institute of Neuroscience and Mental Health, Australia
	Bradley Turner	Florey Institute of Neuroscience and Mental Health, Australia