WesternND

Targeting Western Diet-Induced Neurodegeneration

In the last century, life expectancy in Europe has increased from 44 in 1900 to 80 years in 2020. However, people are living longer but experiencing more years in ill health, with an increase in age-related neurodegenerative diseases. Lifestyle changes have also contributed to a rise in obesity, which is a known risk factor for dementia, and has been linked to chronic inflammation and immune sensitization. To uncover the factors driving chronic inflammatory diseases we have made use of an unbiased large-scale multiomic in vivo screen. Using machine learning techniques we identified that the consumption of Western diet in models of atherosclerosis triggers a change in specific lipids that can bind to the innate immune receptor TLR4. This causes macrophages and microglia, which have a central role in the progression of dementia, to become activated.

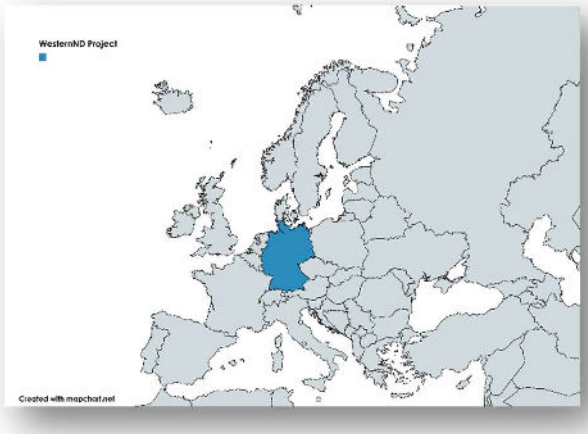
Our Consortium will examine the role of these lipids in driving neuroinflammation and neurodegeneration across human and murine studies using patient cohorts and animal models. Importantly, we ask whether targeting TLR4 signalling could protect against the Western diet-induced changes that lead to dementia. To this end, mice with Alzheimer's disease and Frontotemporal dementia pathology will receive Western diet and TLR4 signalling will be inhibited to block the activity of the circulating lipids. We will prepare microglia from these cohorts for deep sequencing analysis to identify epigenetic and transcriptional changes, which will be functionally tested with RNA therapeutics. In parallel, we will investigate the levels of these lipids circulating in the blood and cerebrospinal fluid (CSF) from patient cohorts with neurodegenerative disease such as Alzheimer' disease, Frontotemporal dementia and atherosclerosis. The immune cells circulating in the CSF of aged atherosclerosis individuals will also undergo sequencing. We will prepare iPSC-derived brain organoids from patients with Alzheimer's disease and Frontotemporal dementia to delineate the role of lipid and TLR4 signalling in driving neuroinflammatory changes in human cells.

Our project aims to uncover the gene pathways and transcriptional networks underlying the Western diet-induced inflammatory changes, while assessing whether the networks are shared across human and murine cells. Importantly, we will identify whether TLR4 or its epigenetic targets can be exploited therapeutically to mitigate the risk of neurodegenerative disease. Our research could highlight lipid signalling as a sensitive biomarker for Alzheimer's disease or Frontotemporal dementia progression, and provide new TLR-associated targets for personalized therapies in dementia.

Total Funding : 1.4 M€

Duration : 3 years

Coordinator : Eicke Latz MD, PhD
✉ : eicke.latz@uni-bonn.de



Consortium Members		
	Eicke Latz MD, PhD	Institute of Innate Immunity, University Hospital Bonn, Germany
	Róisín McManus PhD	
	Musa Mhlanga PhD	
	Wilson F. Abdo MD, PhD	
	Florent Ginhoux PhD	
	Neha Basheer PhD	