BASIC INFORMATION ON SUB-PROJECT

NAME OF PROGRAMME/FUND	Scholarship Fund - Sciex NMS^{ch}
RESEARCH FIELD AND OTHER RESEARCH FIELDS INVOLVED (if applicable)	Basic Biological Research, Basic Medical Sciences
TITLE OF THE SUB-PROJECT	Impact of chronic inflammation on Reelin-mediated signaling and development of AD-like neuropathology (IRAD)
REGION OF THE CZECH REPUBLIC (according to the location of the home institution)	Prague
GRANT AMOUNT SPENT	92 525,53 CHF
INTERMEDIATE BODY	Swissuniversities
HOME INSTITUTION	Charles University, 2nd Faculty of Medicine
HOST INSTITUTION	University of Zurich, Institute of Pharmacology and Toxicology
NAME OF THE FELLOW	Lukáš Rambousek

ABSTRACT OF THE SUB-PROJECT	The importance of inflammatory processes in Alzheimer's disease (AD) has been confirmed by the intensive investigation of inflammatory mediators in the brain of AD patients as well as by the genetic and drug manipulation of animal models of AD. A protein also significantly affected by inflammation is Reelin, a large extracellular matrix protein that controls proper neuronal migration and lamination of cortical structures. In adulthood, Reelin is an important modulator of NMDA receptor-mediated neurotransmission, required for synaptic plasticity, learning and memory. Consequently, abnormal Reelin-mediated signaling has been associated with many human brain disorders involving directly or indirectly altered NMDA receptor function. For most neurological and neuropsychiatric disorders, abnormalities during brain development appear central in the disease etiology. However, a similar causative relationship for neurodegenerative diseases, like AD, has not been investigated yet. Based on the information available, we hypothesise that chronic exposure to pro-inflammatory stimuli will affect Reelin-mediated signaling through misregulation of its proteolytic processing. This is expected to strongly affect NMDA receptor subunit composition and their subcellular localization. This will not only alter its rate of phosphorylation but also impact on amyloid precursor protein (APP) processing and Aβ peptide generation. The aim of the proposed project is to investigate the impact of dysregulated Reelin-mediated signaling on NMDA receptor subunit composition, phosphorylation states and subcellular localization. A particular focus will be the examinations of the different Reelin fragments, mimicking either noncleaving or hyper-cleaving events in order to test whether they differentially affect NMDA receptorassociated functions at adult synaptic sites. Assessments of the effect of pro-inflammatory cytokines on Reelin-mediated signalling are expected to get a better understanding of the molecular mechanisms underlying the inflammation-induced pathophysiology and the development of ADassociated neuropathology.
DATE OF REALISATION OF THE FELLOWSHIP	1.1.2013 - 30.6.2014

MORE INFORMATION ON THE PROGRAMME	**www.sciex.ch**