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Geneeskunde & Farmacie

GF

PhD in Pharmaceutical Sciences
2015-2016

INVITATION to the Public defence of

Eduard-Mihai BENTEA

To obtain the academic degree of **'DOCTOR IN PHARMACEUTICAL SCIENCES'**

Targeting the cystine/glutamate antiporter for neuroprotection: insights from mouse models of Parkinson's disease.

Thursday 26 May 2016
Auditorium **Vanden Driessche**, 17:00
Faculty of Medicine and Pharmacy, Laarbeeklaan 103, 1090 Brussel

How to reach the campus Jette:
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Summary of the dissertation

Parkinson's disease (PD) is an age-related neurodegenerative condition accompanied by disabling motor symptoms. Preventing or delaying the onset of neuronal death in this disorder represents a pending and unmet need. Although various neuroprotective targets have been proposed in pre-clinical studies, none have been validated as yet in patients. A novel therapeutic target recently proposed in PD is system xc-, a membrane cystine/glutamate antiporter. System xc- is induced in pathological conditions and in turn releases high levels of extracellular glutamate, which can become neurotoxic past a certain threshold, triggering 'excitotoxicity'. In the context of the current thesis, we evaluated system xc- as a possible target for neuroprotection in two toxin-based models with distinct mechanisms of action: the intranigral lactacystin mouse model (proteasome inhibition) and the systemic MPTP mouse model (mitochondrial dysfunction). In the first part of the thesis, we characterized the behavioral, neurochemical, and neurodegenerative changes following lactacystin administration in mice as a model of early stage PD. Subsequently, using mutant mice with a genetic deletion of xCT (the specific subunit of system xc-), we investigated the involvement of system xc- in lactacystin- or MPTP-induced loss of nigral dopamine neurons. Our results indicate that absence of system xc- provides age-related neuroprotective effects against lactacystin administration (observed in aged, but not adult mice), but does not influence the neurodegenerative changes following MPTP administration in adult mice (sensitivity of aged mice not investigated). Our findings confirm the involvement of system xc- in PD-related neurodegenerative changes in the ageing brain and support its further development as neuroprotective target.

Curriculum Vitae

Eduard-Mihai Bentea was born on 22nd of April 1987 in Iasi, Romania. Since his early years of education, Eduard developed a particular interest in understanding biochemical and molecular details of cellular systems. In 2009, he successfully completed a Bachelor Degree in Biochemistry in his hometown ("Al. I. Cuza" University, Iasi). Afterwards, he was accepted in a Master of Science program in Biomolecular Sciences at the Vrije Universiteit Brussel (VUB), which he completed in 2011 with the highest distinction. Following his Masters studies, Eduard received a scholarship from Research Foundation Flanders (FWO) to perform a PhD under the promotorship of Prof. Ann Massie and Prof. Ilse Smolders. The work performed during his PhD focused on characterizing a new toxin-based model of Parkinson's disease based on intranigral proteasome inhibition and further exploring system xc- as a possible new target for disease modification. In addition, during this PhD, Eduard had the privilege to visit the lab of Prof. Charles Meshul (Oregon Health & Science University in Portland, Oregon, USA) at several occasions. The time spent abroad was a unique opportunity to learn and apply electron microscopy for studying the ultrastructure of excitatory synapses. Eduard is author of three first-author publications and nine co-author publications in peer-reviewed journals, and presented his work at various national and international conferences.