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MEETING ABSTRACT

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Treatment of APP_{SL} transgenic mice with an ALDH2 activator as a promising treatment option for Alzheimer's disease

Barbara HINTEREGGER[1,2,*], Stefanie FLUNKERT[1], Tobias MADL[2], Jörg NEDDENS[1], Wenjin YANG[3] and Birgit HUTTER-PAIER[1]

[1]QPS Austria GmbH, Grambach, Austria; [2]Gottfried Schatz Research Center (for Cell Signaling, Metabolism and Aging), Division of Molecular Biology and Biochemistry, Medical University of Graz, Austria; [3]Foresee Pharmaceuticals Co., Ltd., Taipei, Taiwan

Background: Alzheimer's disease (AD) is a severe neurodegenerative disorder and early diagnosis of AD is essential to treat the disease as there appears to be no treatment benefit in the fully symptomatic stage. Progressive loss of mitochondrial function or defects in mitochondrial metabolism in the disease can lead to the generation of reactive oxygen species resulting in oxidation of membrane lipids and accumulation of toxic aldehydes such as 4-hydroxy-2-nonenal (4-HNE) in the brain and blood. Additionally, 4-HNE accumulates in the hippocampal region of patients with mild cognitive impairment and patients with early AD. 4-HNE adduction was also found on amyloid proteins and is thought to contribute to amyloid plaque formation in a later stage of the disease. The progressive accumulation of amyloid plaques correlates with neurodegeneration and subsequent atrophy of the affected brain regions. Therefore, a mechanism for rapid clearance of these highly diffusible and harmful aldehydes is crucial to protect cells and tissues from damage. In particular, ALDH2 plays a key role in oxidizing endogenous aldehydic products that arise from lipid peroxidation under oxidative stress. It is therefore possible that diminishing 4-HNE accumulation during the early stages of AD may reduce or prevent the disease progression.

Methods: In this study, male transgenic APP_{SL} mice and non-transgenic littermates received either an ALDH2 activator or vehicle via the drinking water for the duration of four months. We performed behavioral tests, immunohistochemistry as well as untargeted NMR-based metabolic phenotyping of all mice. In this approach, different behavioral tests like the Irwin test, elevated plus maze test, contextual fear conditioning test and Morris water maze test were performed to evaluate general health, anxiety as well as striatal and hippocampal learning, respectively. Immunofluorescent labeling with primary antibodies 6E10, GFAP, Iba-1 and NeuN are performed to quantify plaque load, neuroinflammation and brain atrophy. Untargeted NMR spectroscopy was conducted to monitor perturbations in a large pool of metabolites in serum and tissues like hippocampus, cortex, cerebellum or organs (liver, lung, spleen, heart, kidneys) and reflects changes downstream of genomic, transcriptomic and proteomic fluctuations.

Results: Analysis of all animals in the Morris water maze test revealed a highly significant improvement in spatial learning of ALDH2 activator treated animals compared to vehicle treated animals. Furthermore, we will show histological analyses of the brain of these mice and possible metabolic changes in serum, urine, brain regions like hippocampus, cerebellum and cortex as well as organs analyzed by NMR-based metabolic phenotyping. These results will provide a first insight in the value of this ALDH2 activator for the treatment of AD.

Discussion: By performing behavioral studies, immunofluorescent labeling and NMR-based metabolic phenotyping, we will show whether the ALDH2 activator can ameliorate AD symptoms in the APPSL transgenic mouse model and thus could be an effective drug against AD.

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Keywords: toxic aldehydes – behavioral tests – immunofluorescence – NMR-based metabolic phenotyping

*Corresponding author e-mail: *barbara.hinteregger@medunigraz.at*