Prevention of Amyloidogenic Peptide-Induced Network and Cognitive Deficits by Activation of Peptide Degradation Mechanisms – A Drug Discovery and Translational Project Proposal

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Prevention of Amyloidogenic Peptide-Induced Network and Cognitive Deficits by Activation of Peptide Degradation Mechanisms - A Drug Discovery and Translational Project Proposal

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4

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Research Abstract
Amyloid diseases encompass some of the most devastating conditions such as Alzheimer´s disease (AD), Parkinson´s disease (PD) and Huntington´s disease (HD). Common to all is

cognitive decline in patients and, on the molecular level, the aggregation of disease-typical peptides such as amyloid b-peptide (AD), a-synuclein (PD), huntingtin (HD), and tau (several neurodegenerative diseases). Cognitive decline in patients is paralleled by a decrease of the gamma oscillations and neuronal desynchronization. The cellular mechanisms responsible for this neuronal dysfunction are unclear. Under physiological conditions the brain prevents excessive amyloid formation using defense mechanisms such as BRICHOS domain, or removes excessive peptide through the ubiquitin-proteosomal or the autophagy-lysosomal peptide clearing systems. Whether these protection and clearing mechanisms are actively degraded in AD, PD and HD, or just overwhelmed, is currently unknown. Based on extensive pilot data we will investigate the aggregation process of amyloidogenic peptides and describe the functional consequences on the cellular, synaptic, network and behavioral level. We aim to develop and refine compounds that interfere with peptide aggregation or activate the peptide removal machinery of the cell (proteosome/lysosome) and test whether they are able to prevent and/or rescue the functional impairment on the cellular, synaptic, network and behavioral level caused by peptide aggregation.

Further information available at:

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Investments < €500k

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