COMBINING INDEPENDENT DRUG CLASSES INTO SUPERIOR HYBRID MOLECULES TARGETING ABETA OLIGOMERS

A. Müller-Schiffmann\textsuperscript{1}, J. Maerz-Berberich\textsuperscript{2}, A. Andreyeva\textsuperscript{3}, R. Roenicke\textsuperscript{4}, D. Bartnik\textsuperscript{5}, O. Brener\textsuperscript{6}, A.H.C. Horn\textsuperscript{7}, M. Hellmert\textsuperscript{2}, J. Polkowska\textsuperscript{2}, K. Gottmann\textsuperscript{3}, K.G. Reymann\textsuperscript{4}, S.A. Funke\textsuperscript{5}, L. Nagel-Steger\textsuperscript{6}, C. Moriscot\textsuperscript{8}, G. Schoehn\textsuperscript{8}, H. Sticht\textsuperscript{7}, D. Willbold\textsuperscript{6}, T. Schrader\textsuperscript{2}, C. Korth\textsuperscript{1}

\textsuperscript{1}Department of Neuropathology, University of Duesseldorf, Duesseldorf, \textsuperscript{2}Institute for Organic Chemistry, University of Duisburg-Essen, Essen, \textsuperscript{3}Neuro- and Sensory Physiology, University of Duesseldorf, Duesseldorf, \textsuperscript{4}German Center for Neurodegenerative Diseases, Magdeburg, \textsuperscript{5}Institute for Structural Biology and Biophysics, FZ Jülich, Jülich, \textsuperscript{6}Institute for Physical Biology, University of Duesseldorf, Duesseldorf, \textsuperscript{7}Institute for Biochemistry, University of Erlangen-Nuremberg, Erlangen, Germany, \textsuperscript{8}Institute for Structural Biology Jean-Pierre Ebel, University Joseph Fourier Grenoble, Grenoble, France

Introduction: Cross beta-sheeted oligomeric Abeta is discussed to be a major causative agent for the development of Alzheimers disease and increasingly considered for therapeutical intervention. Rationally designed small molecule beta-sheet breakers are promising compounds proven to prevent or dissolve beta-sheet structures in cell-free in vitro systems. However, due to unspecific binding to Abeta they failed to show convincing effects in vivo.

Aim: The aim of our study was to combine molecular recognition of peptides with functional beta-sheet breaking in novel hybrid compounds to efficiently inhibit Abeta oligomerization.

Methods: Beta-sheet breaking small organic aminopyrazoles were covalently linked to the D-enantiomeric D3 peptide that had been demonstrated to be a potent Abeta binder. Optimization of linker length was done on the basis of molecular dynamics simulations. The functionality of the resulting hybrid compound (JM169) was tested utilizing a cell line secreting oligomeric Abeta. The influence of JM169 on synaptic pathology caused by Abeta oligomers was analysed in two independent electrophysiological assays.

Results: Only JM169 but not its single components or combinations of both prevented the assembly of secreted Abeta. JM169 blocked Abeta induced decrease in mEPSC frequency mediated by AMPA receptors in cultured cortical neurons and impairment of long-term potentiation in hippocampal slices.

Conclusion: We generated a hybrid compound, which selectively reduces naturally secreted oligomeric Abeta and counteracts synaptotoxicity caused by this Abeta form. Moreover we demonstrate that covalent linkage of two entirely different substance classes acting on the same target can yield dramatic synergistic effects and lead to novel pharmacological properties.