

DATE: 10th of May, 2018

SUMMARY of
2017 RESEARCH RESULTS REPORT
For International Collaborative Research with IPR, Osaka University

Research Title		Miniprotein folding, unfolding, misfolding and early stage aggregates
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<p>Summary: Highly insoluble and often toxic oligo- and polymers of cross-β-spines generated fibrils, called as amyloids [Alvaredo <i>et al.</i> 2010] are supramolecular assemblies often associated with conformational diseases and amyloidogenesis. Among the self-assembling protein modules and domains perhaps the smallest one is Trp-cage miniprotein, composed of 20 residues only (Kardos <i>et al.</i> 2015). Miniproteins are oligopeptides with protein-like folding behavior in spite of their relatively small size, enabling to get more easily high-resolution structural information, designed from the C-terminal part of the 39 residue long Exendin-4 (Ex-4), a peptide drug for treating type II diabetes (T2DM). Tc5b (NLYIQWLKDGGPSSGRPPPS) (Neidigh <i>et al.</i> 2002) rapidly (4 μs) and autonomously folds and thus has become an easy-to-handle model for studying protein folding, unfolding. (Hudáky <i>et al.</i> 2008, Rovó <i>et al.</i> 2011, Farkas <i>et al.</i> 2013, Rovó <i>et al.</i> 2013 and 2014) Both Tc5b & Ex-4 are dominated by α-helices and thus, the development of amyloid-like fibrils <i>via</i> β-strand formation is quite unique. The solution state conformation of a suitable, nicely folded polypeptide, containing the entire receptor binding site of Ex-4, responsible for signal transduction <i>via</i> GLP-1R, a B-type GPCR, was studied. The folded, F-, and unfolded, U-states were investigated both by ¹H-NMR and ECD spectroscopy in conjunction with the in-house developed deconvolution algorithm CCA+. The <i>T</i>- and <i>pH</i>-induced misfolding of the same polypeptide is now deciphered. (Horváth <i>et al.</i> 2018, manuscript in preparation). High-field solution state NMR (950MHz) spectra to capture selected I-states of the misfolding pathway were recorded. A larger quantity of double labelled (¹⁵N-, ¹³C-) amyloid was prepared for MAS Solid-State NMR. Amyloid sample centrifuged into the 1mm rotor, MAS measurements were completed, resonances now partial assigned and backbone dihedral angles obtained, currently performing preliminary 3D structure calculations by using the above spectral restrains within program CYANA. Shortly, 3D-structure elucidation will be completed; publication will be finished and submitted.</p>		

***Deadline: May 18, 2018**

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