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Prevention of protein misfolding in Alzheimer's disease by an upgrade of the proteolytic enzyme machinery

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One of the most prominent hallmarks detected in the brains of patients suffering from Alzheimer's disease is the deposition of amyloidogenic plaques. These plaques are largely composed of the amyloid-beta peptide. It has been demonstrated that, even though these plaques comprise an important and recurring feature for disease, that precursor forms of these plaques, called 'oligomers' or 'protofibrils' more potently affect neuronal functioning. Accumulation and subsequent assembly of amyloid-beta peptide into aggregated forms has been reported to be partly brought about by an impaired clearance of the amyloid-beta peptide. Lowering the amyloid-beta peptide burden by increasing clearance provides a promising avenue for treatment of Alzheimer's disease. A number of proteases have been reported to cleave amyloid-beta peptide *in vivo* or *in vitro*. Drug compounds are under development that can modulate enzymatic activity to selectively enhance amyloid-beta peptide degradation. In view of the development of proteolytic-based therapies, more insight into the amyloid-beta peptide-degrading capacity of enzymes is required. For example, the effect of amyloid-beta proteolytic enzymes on various misfolded forms of the peptide has been little documented in the literature. Also the effect of in vivo occurring combinations of enzymes has not been explored. Moreover, the properties of enzyme-induced fragments from Aβ are currently unknown. To extend our understanding of the potential therapeutic utility of amyloid-beta peptide proteolytic enzymes, we investigated enzyme-mediated cleavage of amyloid-beta peptide *in vitro* using biophysical and biochemical assays and we identified new cleavage sites, cooperative activity of enzymes and characterized the potential aggregation behavior of resulting fragments.

Biography

Kerensa Broersen-Nutma completed her Doctorate in the field of Protein Aggregation at Wageningen University in The Netherlands in 2005. After her Postdoctoral study at the MRC-LMB in UK, she joined the Free University of Brussels (VUB), Flanders Institute for Biotechnology (VIB) in 2007. She headed a research team that studied the molecular mechanism of Alzheimer's disease. This led to the discovery of molecular pathways of a number of risk factors that affect Alzheimer's disease pathobiology. Subsequently, she joined the Nanobiophysics Group at the University of Twente/MIRA Institute in The Netherlands as an Assistant Professor investigating further the impact of protein structures on human health with her team.

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