Neurodegeneration in AD has been linked with early deposition of Abeta oligomers at synapses. Recent studies have shown that Abeta post-translational modifications including, pyroglutamate (pE) formation could accelerate oligomerization and neurotoxicity. However, the patterns of distribution and time-course of appearance of these toxic Abeta species is not completely understood.

For the present study, we generated monoclonal antibodies against (pE)-modified (D129) and unmodified Abeta (3A5) and investigated the location in the brains of patients with various stages of AD and in APP transgenic (tg) mice.

Immunocytochemical analysis in the brains of patients with MCI and Braak stage I-III showed that D129 recognized granular deposits in the neuropil as well as micro-plaques distributed around axons and dendrites. D129 punctuate immunostaining co-localized with PSD95. Such deposits were not identified with the 3A5 antibody. In later stage AD cases, at Braak stages IV-VI, the antibody D129 recognized diffuse and dense amyloid deposits both with a granular or fibrillar appearance. Similarly, in two APP tg mice (mThy1-mutant APP751: line 41 and Tg2576) at early stages D129 recognized granular deposits in the neuropil that co-localized with PSD95. At later stages (pE)-Abeta immunostaining was associated with diffuse and dense plaques. In brains of APP tg mice and AD cases, intracellular staining was only detectable using the 3A5 antibody, but not with the D129 antibody.

Taken together, our results indicate that (pE)-Abeta accumulates early in the pathogenesis of AD around synapses. At later stages (pE)-Abeta can be found in micro-plaques that can serve as nucleus of amyloidogenic aggregation.