Cellular models for amyloid-β toxicity

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One of the hallmarks of Alzheimer's disease (AD) is extracellular deposition of senile plaques, composed primarily of aggregated β-amyloid (Aβ) peptide. Although Aβ is involved in the pathogenesis of AD, not much is known about the cellular mechanisms underlying Abeta toxicity in neurons.
We aim to study the molecular mechanisms of toxicity of Aβ in neuroblastoma cells. By comparing the effects of intracellular Aβ in these cells and extracellular addition of synthetic Aβ to these cells we aim to study the role of subcellular localisation. In addition we want to study in detail the role of physico-chemical properties of Aβ in its toxicity.
For studying toxicity of intracellular Aβ, we will use different cellular models: 1) neuroblastoma cell lines overexpressing wildtype APP and an FAD mutant APP, 2) neuroblastoma cell lines expressing ER-targeted Aβ. Using these models we can study the toxicity of Aβ related to its subcellular localisation.
Studying the cellular effects of extracellular Aβ, we also aim to compare the effects of fibrillar *vs.* oligomeric Aβ, since several studies have shown that the initial oligomers of Aβ, rather than the highly structured (fibrillar) aggregates are cytotoxic.
For studying the toxicity of extracellular Aβ, we will use different synthetic forms of Aβ: 1) fibrillar forms of Aβ and 2) oligomeric forms of Aβ (in cooperation with Technical University Eindhoven). Using these extracellular Aβ models, we can study the toxicity of extracellular Aβ and its interaction with associated proteins related to the aggregation status of Aβ. Additionally, this approach will give us detailed information about the physico-chemical properties of Aβ in relation to its biological actions.
These different cellular models will provide new information on the cellular mechanisms involved in Aβ mediated neurotoxicity.

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