Identifying Dyes Selective for Aβ42 Oligomers as Ligands for PET Probes in Alzheimer's Disease

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There are multiple lines of evidence implicating small, globular oligomers as the dominant molecular toxins initiating the cascade of events resulting in Alzheimer's Disease. Yet, providing solid evidence to support or dismiss this oligomer hypothesis has been challenging. Progress has been hampered by several basic obstacles related to generating amyloid oligomers as binding targets for indicators. As a result, there is a lack of assays for detecting oligomers in vivo, let alone monitoring their spatio-temporal evolution in patients.

Our laboratory has developed an in vitro kinetics assay for identifying fluorescent dyes with selectivity for Aβ42 oligomers over fibrils (AβFs). Several potential candidates emerging from this screen were evaluated for their continued target engagement and selectivity in mouse models of AD as well as AD brain tissues. In this talk we will present the principle of our two-step screening process as well as the current lead candidate emerging from this two-step screening process. The main goal of this project is to identify dyes selective for AβOs oligomers which can serve as small molecule ligands for development into oligomer-selective PET probes. In vivo PET imaging of Aβ oligomers would provide the missing tool to elucidate the role of oligomers in AD, offer early-stage diagnostics, and provide a quantitative assay for evaluating pharmacological interventions targeting Aβ oligomers.

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