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## Fluorescent derivatives of the amyloid ligand Congo red for the detection of A $\beta$ and Tau aggregates

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**Statement of the Problem:** Alzheimer's disease (AD) is the most common neurodegenerative disorder of the brain and a leading cause of dementia. A $\beta$  plaques consisting of A $\beta$  peptides and Neurofibrillary Tangles (NFTs) consisting of hyperphosphorylated Tau has been recognized as the main two pathological hallmarks of AD. Investigation of Congo red led to the discovery of bis-styrylbenzenes as a class of compounds with strong A $\beta$  plaque binding properties.

**Methodology & Theoretical Orientation:** Starting from the amyloid ligand X-34, A $\beta$ -fibril and Tau fibril binding affinities and specificities for the four fluorescent derivatives of X-34 were determined by means of fluorescence titrations with A $\beta$ 1-42 and Tau fibrils, respectively and a fluorescence assay using human AD brain sections.

**Findings:** The five ligands can bind to A $\beta$ 1-42 and Tau fibrils with augmented intensities, respectively, but with very weak fluorescence changes in the presence of A $\beta$ 1-42 oligomer and monomer. Benzene and naphthalene derivatives upon binding to A $\beta$ 1-42 fibrils showed significantly increased quantum yields (QY). The thiophene derivative in buffer displayed high QY compared with the other probes, while quinoxaline and benzo[c][1,2,5]thiadiazole derivatives showed very low QY in the absence/presence of A $\beta$ 1-42 fibrils. The two pathological hallmarks, A $\beta$  plaques and NFTs, could be readily identified due to bright fluorescence especially quinoxaline derivative, specifically stain A $\beta$  plaques.

**Conclusion & Significance:** The central benzene motif of X-34 can be replaced with other heterocyclic moieties without reducing the ligands' selectivity. However, the quinoxaline derivative can selectively detect A $\beta$  plaques and not NFTs. We foresee that these ligands will be useful candidate markers for monitoring the formation and progression of a variety of disease-associated protein aggregates.



### Biography

Jun Zhang has his expertise in designing and synthesizing small fluorescent ligands for the identification of protein aggregates, the common pathological hallmark of many neurodegenerative diseases such as Alzheimer's and Parkinson's disease (AD and PD). These novel ligands will expand the tool box of fluorescent ligands for *in vitro* monitoring of amyloid fibril formation and *in vivo* monitoring of progression and deposition of various disease-associated proteins.

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