Docket #: S25-472

Q-DOAS: A Quantitative Assay for Detection of Protein Aggregates and Oligomers in Neurodegenerative Disease

Stanford scientists have developed Q-DOAS (Quantitative Detection of Oligomer and Amyloid Seeds), a plate reader-based fluorescence quenching assay designed to track the formation of early-stage toxic oligomers and amyloid seeds in real-time. Unlike traditional methods that only detect large, late-stage amyloid fibers, Q-DOAS provides a high-resolution window into the formation of small, soluble oligomers—the species increasingly recognized as the primary drivers of neurodegenerative toxicity.

Neurodegenerative diseases such as Alzheimer's, Parkinson's, and Huntington's are driven by the accumulation of toxic protein aggregates. Current diagnostic standards, such as the Thioflavin T (ThT) assay, rely on the presence of cross-? sheet structures found in mature fibers. Consequently, they cannot detect early-stage "seeds" and non-amyloid oligomers that lack these structures. Furthermore, existing seeding assays often require multiple rounds of kinetic amplification, which can be difficult to standardize and quantify accurately.

Q-DOAS overcomes these limitations by utilizing site-specific, self-quenching fluorescent labeling dye. As labeled monomers interact and form oligomers or aggregates, dye molecules come into close proximity and quench each other's fluorescence signal. By monitoring this decrease in fluorescence in real-time, Q-DOAS directly tracks the depletion of the monomer pool. This allows for the precise, mathematical quantification of seeding activity and aggregation kinetics in complex biological samples, including cell lysates and animal models.

Stage of Development: Proof of concept - in vitro

Applications

- Quantitative screening of small molecule and protein-based aggregation inhibitors for neurodegeneration drug discovery
- Detecting and staging disease burden in clinical samples (e.g., CSF, blood, or tissue lysates) by measuring seed concentration.
- Monitoring therapeutic efficacy in clinical trials for neurodegenerative disease.

Advantages

- Higher sensitivity to early-stage, non-amyloid oligomers
- Direct, fully quantitative kinetic readout of monomer-to-aggregate conversion
- Broad compatibility to any aggregation-prone protein by optimizing the fluorophore placement.

Publications

- Kleczko, K. M., Gestaut, D., et al. (2025). Q-DOAS: quantitative detection of oligomer and amyloid seeds. *Unpublished Manuscript.*

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