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Cyclic Peptides as Modulators of Tau Aggregation: A High-throughput Screening Approach

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Proteins lacking stable tertiary and/or secondary structure, known as intrinsically disordered proteins (IDPs), play crucial roles in both physiological and pathological processes. Among them, tau, an IDP linked to neurodegenerative diseases such as Alzheimer's, undergoes liquid-liquid phase separation (LLPS) and aggregation, forming neurotoxic oligomers and fibrils. This work employs a high-throughput bacterial platform to screen 10,104,000 small cyclic for their ability to inhibit tau aggregation. To monitor protein aggregation inside E. coli, tau was fused to green fluorescent protein (GFP). Overexpressing tau-GFP in bacteria results in aggregation and loss of fluorescence, while successful inhibition by a peptide restores the fluorescence. Fluorescence-activated sorting of the most fluorescent cells and next-generation sequencing identified the effective peptides in modulating tau solubility. Biophysical methods are employed to gain insights into the binding, the activity, and the effect of the most promising peptides. Finally, the most promising candidates will be validated in Drosophila melanogaster, a relevant disease model, to assess their in vivo efficacy. This integrative approach, combining high-throughput screening with biophysical characterization, provides a powerful platform for developing novel aggregation modulators, targeting tau in neurodegenerative diseases.