

Defining Minimal Mechanisms Of Tau Aggregation: Disease-Relevant Mutations Recapitulate Structural Motifs Of Tauopathies



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Tauopathies like AD, CBD, LNT, and PSP are driven by disease-specific tau fibril conformations that have historically been difficult to reproduce in vitro, limiting diagnostic and therapeutic development. To address this, we designed synthetic "mini-tau" peptide constructs that self-assemble into stable, reproducible fibrils recapitulating disease-associated structural motifs confirmed by cryo-EM. Disease-relevant mutations (P301L, S305I) altered both fibril structure and seeding behavior, demonstrating residue-level control over conformation and function. These synthetic fibrils efficiently template full-length tau misfolding, reproduce key PET ligand binding characteristics across multiple tauopathies, and offer a scalable, patient-material-free platform to accelerate ligand screening, antibody development, and therapeutic discovery.

INTRODUCTION

METHODS

RESULTS

CONCLUSIONS

REFERENCES

