Chaperone triaging on the fate of aggregating proteins.

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Introduction

We aim to uncover the molecular mechanism governing the decision between refolding and degradation. The conserved Hsp70-Hsp90 chaperone axis acts as a central node in this process, shuttling misfolded substrates between refolding, reactivation, or degradation. This creates a regulatory window for co-chaperones to modulate client fate, yet the molecular rationale of this decision-making remains unclear. Using aggregation-prone substrates, such as α-synuclein fibrils and misfolding-prone proteins, we aim to dissect the disaggregation capacity of the chaperone network in human vs. artificial samples, study the influence of specific chaperone-co-chaperone interactions on triage outcomes, and develop methodologies to steer the chaperone triaging decision towards disaggregation and degradation.

Quantifying α-synuclein aggregation

Key Method:

Figure 1: Graphical representation of FIbrilRuler method developed in our group, used to study aggregation of α-synuclein. The Amyloid fibril structure is recreated from Cryo-EM analysis of Parkinson's disease patient brains pdb:8fpt. RFU - relative fluorescence intensity

Key Results:

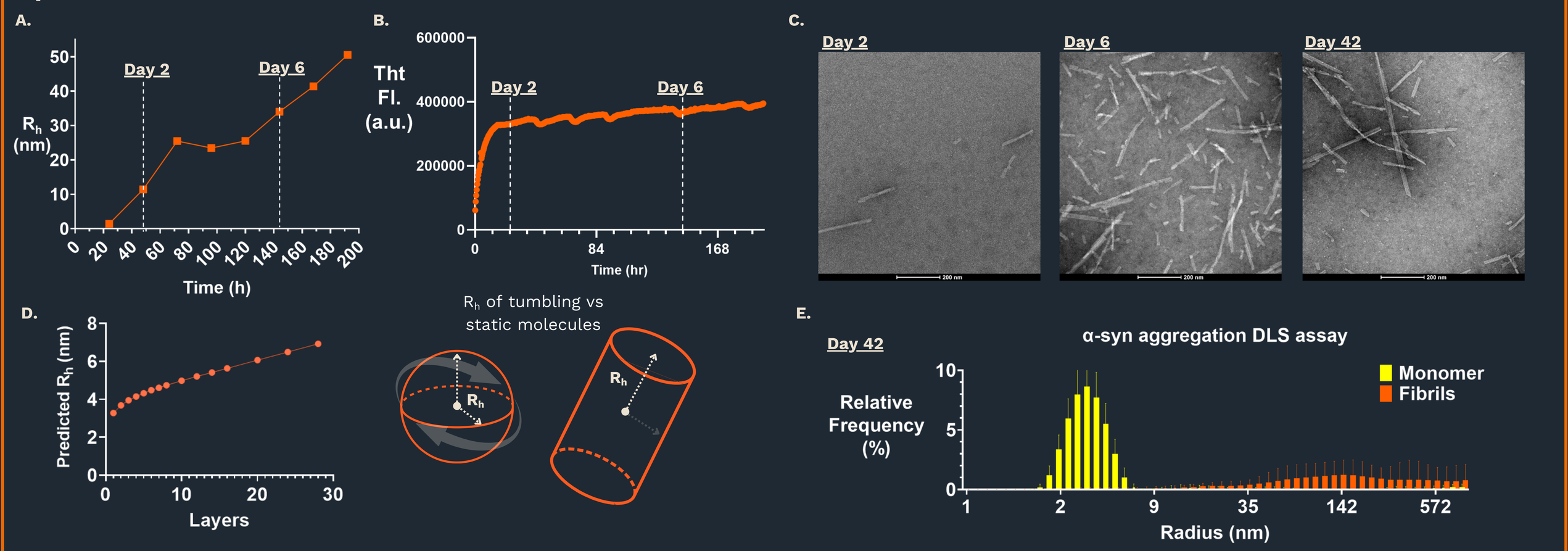

Figure 2: Quantifying α-synuclein aggregation using: A. FibrilRuler assay B.Tht assay. C. Negative staining EM analysis. E. DLS analysis. D breaks down relationship of Hydrodynamic radius to proportional fibril length.

Future Projects.

Study of Disaggregation via Hsp70 chaperone system

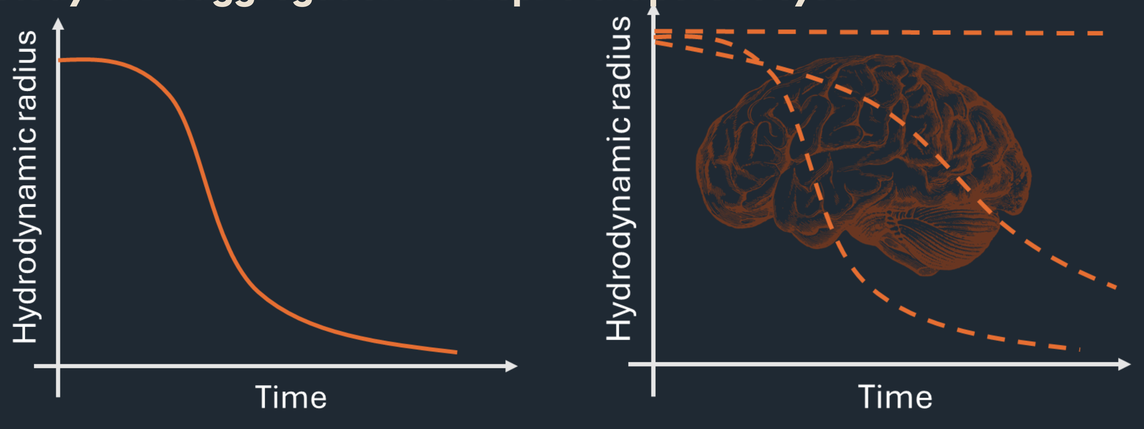

Figure 3: Graphical representation of dissaggregation of synthetic Amyloid Fibril vs Patient Material

Study of Amyloid Fibril Degradation by 26S proteosome

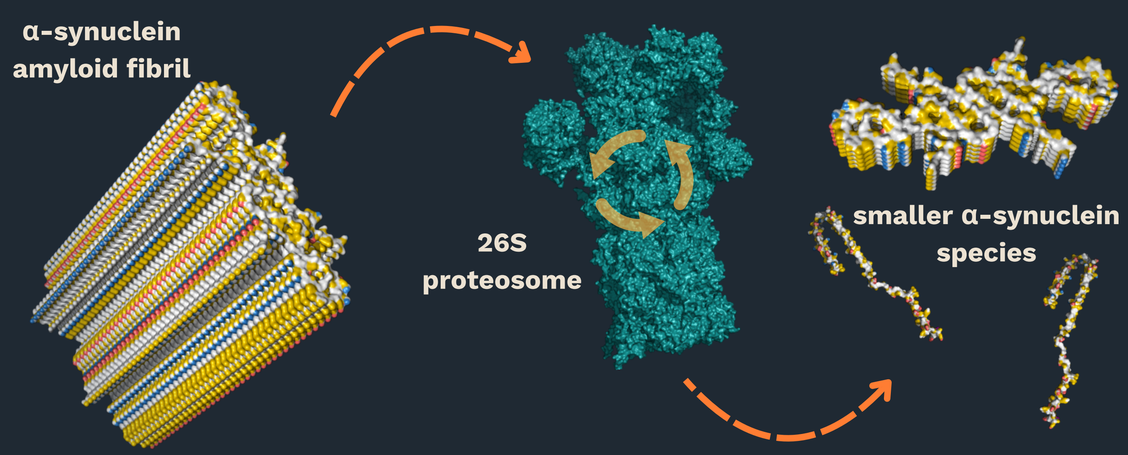

Figure 4: Graphical representation of 26S proteasomal degradation of Amyloid fibrils

Development of FPJ constructs.

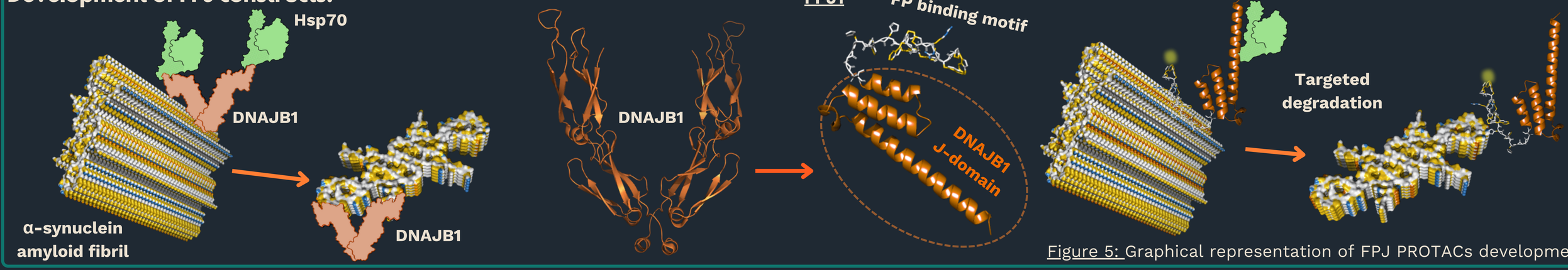

Figure 5: Graphical representation of FPJ PROTACs development.

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References
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