

Disrupting the α -Synuclein–ClpP Axis: A Mitochondrial-Targeted Therapeutic Strategy for Parkinson's Disease

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Mitochondrial dysfunction and α -synuclein (α Syn) accumulation are two defining hallmarks of Parkinson's disease (PD), yet the mechanistic connection between them remains underexplored. Our recent work identifies the mitochondrial matrix protease ClpP as a critical mediator in this pathogenic axis. We show that pathological α Syn, including the familial A53T mutant, directly binds to and impairs ClpP function, disrupting mitochondrial protein quality control and promoting oxidative stress, bioenergetic failure, and neurodegeneration. This interaction was observed in PD patient-derived neurons, animal models, and human postmortem tissue. To therapeutically target this interaction, we developed a novel decoy peptide, CS2, that binds the NAC domain of α Syn and blocks its association with ClpP. CS2 treatment restores mitochondrial function, reduces α Syn aggregation, and improves motor and cognitive function in multiple preclinical PD models. These findings define the α Syn–ClpP interaction as a novel driver of PD pathogenesis and highlight CS2 as a promising mitochondria-targeted therapeutic candidate for synucleinopathies.

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