Conference Proceedings By
United Research Forum, London, UK

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World Congress on

Dementia, Alzheimer's, Parkinson's & Neurodegenerative Disorders

July 09-10, 2026 | Frankfurt, Germany

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Targeting alpha-synuclein with the lipoxygenase inhibitor PTC-041 as a therapeutic approach for the treatment of Parkinson's disease

Parkinson's disease (PD) is a common neurodegenerative disorder in which α-synuclein aggregation and neuronal dysfunction are central pathological features. Ferroptosis, a regulated cell-death pathway driven by iron-dependent lipid peroxidation (including 15-lipoxygenase activity), has been implicated in PD and may contribute to synucleinopathy. We evaluated the therapeutic potential of PTC-041, an anti-ferroptotic lipoxygenase inhibitor, to mitigate lipid peroxidation, ferroptotic cell death, α-synuclein pathology, and functional deficits across PD-relevant models. PTC-041 was assessed in primary human PD patient-derived fibroblasts, primary rat neuronal co-cultures, and engineered immortalized rat dopaminergic neuronal cells for effects on viability, lipid peroxidation, and α-synuclein aggregation-related outcomes. In vivo efficacy was evaluated in Line 61 mice overexpressing human α-synuclein (aggregation/phosphorylation and proteomic markers of neuronal health) and in the 6-hydroxydopamine (6-OHDA) hemiparkinsonian rat model (motor deficits). PTC-041 potently protected PD patient fibroblasts from lipid peroxidation and subsequent ferroptotic death, prevented ferroptosis-related neuronal loss and astrogliosis in primary rat neuronal cultures, and inhibited ferroptosis-associated α-synuclein aggregation and nitrosylation in cell models. In Line 61 mice, PTC-041 reduced α-synuclein aggregation and phosphorylation and preserved neuronal and non-neuronal cell populations, supported by maintenance of neurofilament markers; proteomics indicated rescue of synaptic and cytoskeletal proteins required for NMDA-receptor function. Finally, PTC-041 protected against 6-OHDA–induced motor deficits in rats. These findings support continued development of PTC-041 and related lipoxygenase inhibitors as a disease-modifying strategy targeting ferroptosis-linked, pathogenic α-synuclein biology in PD.

Keywords: Parkinson's diease, ferroptosis, α-synuclein, 15-lipoxygenase, lipid peroxidation

Biography

Dr. Angela Minnella is the Director of Neuroscience at PTC Therapeutics, where she leads research efforts focused on developing innovative therapies for neurological and neurodegenerative disorders. With extensive experience in neuroscience and translational research, she oversees scientific programs that integrate molecular biology, pharmacology, and disease modeling to advance potential treatments from discovery through preclinical development.

Throughout her career, Dr. Minnella has contributed to research aimed at understanding the biological mechanisms underlying disorders of the central nervous system and identifying novel therapeutic strategies. Her work emphasizes the translation of fundamental scientific discoveries into targeted therapies, supporting the development of medicines designed to address unmet medical needs and improve outcomes for patients with rare and complex neurological diseases.

doi.org/10.51219/URForum.2026.Angela-Minnella

ISBN: 978-1-917892-37-7