

Role of Microbiota Derived Short Chain Fatty Acids in α -Synuclein Aggregation and Seeding

Giulio Pasinetti^{1*}, Risham Singh² and Lap Ho²

¹Mount Sinai School of Medicine, USA

²Icahn School of Medicine at Mount Sinai, USA

Objective: To determine whether microbiome derived short chain fatty acid (SCFA) may modulate abnormal α -synuclein misfolding and seeding activity of α -synuclein to support the hypothesis of potential novel therapeutic approaches.

Background: There is growing evidence from both *in vivo* and *in vitro* studies that in many neurodegenerative disorders, including synucleinopathies, cell-to-cell transmission of a pathological, misfolded protein occurs and may be a vehicle for spreading of pathology throughout the brain. We hereby investigate whether microbiota-derived SCFAs may help attenuate the misfolding of α -synuclein and their effects on seeding synucleinopathy.

Design/Methods: *In vitro* aggregation of α -synuclein in the absence or in the presence of SCFAs at a molar ratio of 1:1 or 1:4 α -synuclein:SCFA, were monitored by using independent assays: photo-induced cross-linking of unmodified proteins assay, thioflavin-T, fluorescence assay, or electron microscopy.

Results: We found that select microbiome-derived SCFAs significantly interfere with α -synuclein aggregation in independent *in vitro* assays.

Conclusions: Select microbiome-derived SCFAs may help protect against diverse synucleinopathies by converting dietary fibers into biologically available SCFAs which significantly interfere with aggregation of disease-specific α -synuclein into toxic aggregates. Ongoing cell-based systems, which detect levels of α -synuclein by fluorescent FRET signaling, will clarify the impact of this anti-aggregation activity of SCFAs on interference of α -synuclein seeding activity that is critical for the propagation of α -synuclein mediated pathologies. This data will help to clarify distinct α -synuclein seeding activity from α -synuclein isolated from post-mortem brain samples of patients with Parkinson's disease, multiple systemic atrophies, and other synucleinopathies, leading to novel therapeutic approaches.

Biography:

Dr. Giulio Maria Pasinetti is the Saunders Family Chair and Professor of Neurology at the Icahn School of Medicine at Mount Sinai. He is the Program Director of the Center on Molecular Integrative Neuroresilience. The primary goal of the Center grant is understand the molecular mechanisms and pathophysiology that may be at the basis of stress-induced mood disorders, which are major risk factors for acceleration of age-related Alzheimer's disease and other forms of dementia. Dr. Pasinetti's Center is currently testing novel brain bioavailable bioactive "phytodrugs" that have been characterized by the Center in experimental models of disease in translational Alzheimer's disease preventative trials.