

Systems Biology Analysis of Synucleinopathies

Citation for published version (APA):

Greally, S. (2024). *Systems Biology Analysis of Synucleinopathies: 'A Mass Spectrometry-based Proteomics Study of Parkinson's Disease, Dementia with Lewy Bodies, and Multiple System Atrophy'*. [Doctoral Thesis, Maastricht University]. Maastricht University. <https://doi.org/10.26481/dis.20241125sg>

Document status and date:

Published: 01/01/2024

DOI:

[10.26481/dis.20241125sg](https://doi.org/10.26481/dis.20241125sg)

Document Version:

Publisher's PDF, also known as Version of record

Please check the document version of this publication:

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Sinead-Greally PhD Thesis

Propositions

1. Mass spectrometry offers a powerful tool for discovering both common and divergent molecular pathways in synucleinopathies, aiding in the development of targeted diagnostic and therapeutic strategies.
2. The unique molecular alterations observed in Parkinson's disease (PD), Dementia with Lewy bodies (DLB), and Multiple System Atrophy (MSA)—such as increased APOE and amyloid-beta in DLB, immune system dysregulation in PD, and mitochondrial dysfunction in MSA—highlight the need for disease-specific biomarkers and therapeutic approaches tailored to the molecular characteristics of each disorder.
3. Inclusion of Multiple System Atrophy in proteomic studies is essential for uncovering unique molecular mechanisms, contributing to a more comprehensive understanding of synucleinopathies.
4. Proteomic analysis of Dementia with Lewy bodies suggests that elevated tau levels may define a

distinct subgroup on the synucleinopathy-tauopathy spectrum, with important implications for disease classification and treatment.

5. The combination of mass spectrometry, deep-visual and single-cell proteomics will revolutionize neuroscience by enabling the discovery of cell-type-specific protein alterations in neurodegenerative diseases.
6. Rodent models are essential tools in neurodegeneration research and preclinical drug development, but their effectiveness hinges on detailed molecular characterization to ensure accurate translation of results to human disease.
7. The future of neurodegenerative disease treatment lies in using a multipronged approach where the combination of small molecules and biologics, such as antibodies targeting specific pathological proteins, would achieve a comprehensive disease treatment.
8. By identifying novel therapeutic targets in neurodegenerative diseases, this research lays the groundwork for future drug development, offering

hope to our aging populations facing an increasing prevalence of these conditions.

9. "You don't have to see the whole staircase, just take the first step." — Martin Luther King Jr.