Keynote Forum

7th International Conference on

Parkinson's & Movement Disorders

November 11-12, 2019 | London, UK

Rebecca Dyanne Wooten

Wooten-Analytics, USA

A researcher's perspective on Parkinson's disease

There are many key factors that contribute to the onset of Parkinson's disease. One contributing factor is heredity. In an article I contributed to entitled On Heredity Factors of Parkinson's

Disease: A Parametric and Bayesian Analysis, we modeled the chances or likelihood of an individual developed Parkinson's disease and using real world data in conjunction with Maximum Likelihood Estimation and Bayesian Analysis, it was shown that age, family history, and gender are contributing factors. However, and moreover, it was shown that environmental factors and head trauma are also significantly contributing factors. This leads to assessments of risk factors and the possibility of early detection. Two key priorities are early detection and treatment. Suggested risk factors, in addition to gender include age, race and ethnicity. We discuss the issues that arise when as a data scientist, the analysis of the data reveal incomplete and/or dirty data.

Biography

Rebecca Dyanne Wooten is a Researcher and Data Analyst who has been being treated for Parkinson's disease since 2012. She has, since the start of her treatment begun seeking data to help her better understand what caused the early onset of Parkinson's and to learn how to find balance and manager her condition. She has been a reviewer for the Michael J. Fox Foundation, has worked with an intern (now working at Tampa General Hospital) and contributed to articles on the topic of Parkinson's disease. Her primary area in theoretical statistics is regression and she has developed new methods of regression that model codependent relationships extending standard regression to implicit regression which includes non-response analysis and rotational analysis.

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Matthew A Cooper

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Inzomelid is a CNS penetrant anti-inflammatory drug that blocks NLRP3 inflammasome activation targeted to prevent Synuclein Pathology and Dopaminergic Degeneration in Parkinson's disease

Fibrillar synuclein is implicated in cell-to-cell transmission and neuronal degeneration in Lewy body diseases, but mechanisms linking synuclein pathology and dopaminergic neuronal loss to chronic microglial neuroinflammation have not been defined. We show that activation of the microglial NLRP3 inflammasome is a common pathway triggered by both fibrillar synuclein and dopaminergic degeneration in the absence of synuclein aggregates. Cleaved caspase-1 and the inflammasome adapter protein ASC are elevated in the substantia nigra and plasma of Parkinson's patients, and in multiple preclinical Parkinson's models including 6-hydroxydopamine, MitoPark, and the preformed fibril model of synuclein pathology.NLRP3 activation by fibrillar synuclein in microglia results in a delayed, but robust activation of the NLRP3 inflammasome, with substantial extracellular IL-1β and ASC release in the absence of pyroptosis. Nanomolar doses of the potent small molecule tool compound NLRP3 inhibitor, MCC950, or the clinical stage investigative drug Inzomelid, abolished fibrillar synuclein-mediated NLRP3 activation and extracellular ASC release. Further, Inzomelid is active in the central nervous system following oral dosing, and can mitigate inflammasome activation, motor deficits and nigrostriatal dopaminergic degeneration. Crucially, chronic NLRP3 inhibition effectively blocks fibrillar synuclein mediated motor deficits, dopamine loss and pathological synuclein spread in vivo. These findings suggest that the microglial NLRP3 inflammasome may be a sustained source of neuroinflammation that drives progressive neuropathology in Parkinson's and highlight Inzomelid as a potential disease-modifying therapeutic target for Parkinson's.

Biography

Matthew A Cooper is co-founder and CEO of Inflazome, co-founder and Director of Defensin Therapeutics, Affiliate Prof. in Biochemistry at Trinity College Dublin, Prof. Chemical Biology at the University of Queensland, Director of the Center for Open Antimicrobial Drug Discovery (CO-ADD) and the IMB Center for Superbug Solutions. He was the founder and Managing Director of Cambridge Medical Innovations (now part of Abbot) and CSO and co-founder of Akubio. He has worked in tools companies, diagnostics and therapeutics in the areas of drug screening and drug design, infectious diseases, innate immunity and the microbiome, and has consulted with AdProTech, Alere, Apax Capital Partners, AstraZeneca, Cambridge Antibody Technology, DeNovo Pharmaceuticals, Ellume, GE Healthcare, Heptares Therapeutics, Ionian Technologies, Inverness Medical Australia, NxP Semiconductor, OSI Pharmaceuticals, Pfizer, Protein Mechanics, Respirio, Science Foundation Ireland, Sense Proteomics/Procognia and Solexa (now Ilumina).

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José Luis Lanciego Pérez

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Glucocerebrosidase Gene Therapy for Parkinson's disease

Mutations in the GBA1 gene coding for the lysosomal enzyme glucocerebrosidase (GCase) are related to increased incidence of synucleinopathies such as Parkinson's disease (PD) and dementia with Lewy bodies (DLB). Although the mechanisms through which GCase regulates the homeostasis of alpha-synuclein still are not fully understood, the identification of reduced GCase lysosomal activity as a common feature sustaining the neuropathological findings underlying PD and DLB -even when considering sporadic forms of these synucleinopathies- has recently attracted strong interest in the field. Accordingly, a number of novel strategies focused on increasing GCase activity to reduce alpha-synuclein burden and preventing dopaminergic neuronal death have been designed. Here we have performed bilateral injections of a recombinant adeno-associated viral vector serotype 9 coding for the mutated form of human alphasynuclein (rAAV9-SynA53T) for disease modelling purposes, both in mice as well as in nonhuman primates (NHPs), further inducing a progressive neuronal death in the substantia nigra pars compacta (SNc). Next, another rAAV9 coding for the GBA1 gene (rAAV9-GBA1) was unilaterally delivered in the SNc of mice and NHPs one month after initial insult with rAAV9-SynA53T, together with the contralateral delivery of an empty rAAV9 (rAAV9-null) for control purposes. Obtained results showed that rAAV-mediated enhancement of GCase activity reduced alpha-synuclein burden, leading to improved survival of dopaminergic neurons together with a reduction in microglial-driven pro-inflammatory phenomena. Furthermore, the trans-synaptic "prionlike" spread of mutated alpha-synuclein was impeded upon treatment with rAAV9-GBA1. Data reported here support the use of glucocerebrosidase gene therapy as a disease-modifying treatment for PD and related synucleinopathies, also including sporadic forms of these disorders.

Biography

José Luis Lanciego Pérez is currently ahead of the Functional Neuroanatomy of Basal Ganglia Lab at the Center for Applied Medical Research, University of Navarra. He has been working in the field of basal ganglia-related neurodegenerative disorders for more than 20 years. He has published more than 100 papers in indexed journals, with an H index of 35 (May, 2019). In December 2006, his group received the credentials of "group of excellence" in the field of neurodegenerative disorders, issued by the Spanish Ministry of Health. At present, his research group has a narrow focus on the implementation of a number of different gene therapy strategies targeting neurodegenerative disorders caused by the pathological aggregation of misfolded proteins.

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Role of Neuromelanin in Parkinson's disease

Statement of the Problem: In Parkinson's disease (PD), there is a preferential degeneration of melanin-containing neurons, in particular dopaminergic neurons of the substantia nigra (SN). Loss of nigral neurons results in the typical motor symptoms of the disease, which constitute the cardinal clinical diagnostic criterion for PD. However, the potential contribution of neuromelanin to PD pathogenesis remain elusive because, in contrast to humans, common laboratory animals, such as rodents, lack neuromelanin.

Methodology & Theoretical Orientation: Unilateral vector-mediated expression in rat of human tyrosinase (hTyr), rate-limiting enzyme for the synthesis of peripheral melanins, resulted in an age-dependent production of neuromelanin within nigral dopaminergic neurons. Neuromelanin levels in rat where comparable to those reached in elderly humans, allowing for the first time to assess *in vivo* the consequences of progressive neuromelanin accumulation.

Findings: Accumulation of neuromelanin above a specific threshold ultimately compromised neuronal function and led to an age-dependent PD phenotype comprising nigrostriatal neurodegeneration, hypokinesia, impaired dopamine release and Lewy body-like inclusion formation. In humans, both PD patients and pre-symptomatic subjects reached this pathogenic threshold of intracellular melanin, in contrast to control healthy brains. At the molecular level, decreases in both autophagic and ubiquitin-proteasome degradation system activities pointed to a general failure of cellular proteostasis. Indeed, enhancement of lysosomal proteostasis by overexpressing the transcription factor EB (TFEB) reduced neuromelanin levels and prevented neurodegeneration in tyrosinase-expressing animals.

Conclusion & Significance: Our results reveal a novel pathogenic scenario in PD, in which the continuous, age-dependent build-up of neuromelanin within autophagic compartments may ultimately exhaust the vesicular storage capacity of the cell when reaching a certain threshold of accumulation, imparting general proteostasis in the cell. Modulation of neuromelanin accumulation may thus provide unprecedented therapeutic opportunities for PD and brain aging.

Biography

Iria Carballo-Carbajal has long expertise in studying the cellular mechanisms underlying neurodegeneration in Parkinson's disease (PD). In the last years, she has extensively investigated the molecular bases involved in LRRK2-associated pathogenesis as well as in the regulation and pathological spreading of alpha-synuclein using different cell-based, iPSC-derived and *in vivo* animal models. Her current research interest focuses on the potential role of neuromelanin in PD. A major contribution has been the generation of the first *in vivo* model of melanized *substantia nigra* in rodents, showing that progressive accumulation of this dark pigment with age can finally lead to a parkinsonian phenotype, which reproduces main motor, functional and neuropathological features observed in patients. These results, recently published in Nature Communications, may open the door to new therapeutic avenues and to a paradigm shift in the field.

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