Pacific Parkinson's
RESEARCH INSTITUTE

2022 IMPACT REPORT

Microbiome in Parkinson's Disease

The Pacific Parkinson's Research Institute (PPRI) partners with the UBC Faculty of Medicine to fund the strategic research priorities of the Pacific Parkinson's Research Centre (PPRC), a Canadian Centre for Excellence for the diagnosis and management of Parkinson's disease and related disorders.

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The Pacific Parkinson's Research Institute (PPRI) partners with the UBC Faculty of Medicine to fund the strategic research priorities of the Pacific Parkinson's Research Centre (PPRC), a Canadian Centre for Excellence for the diagnosis and management of Parkinson's disease and related disorders. This partnership enables our world-leading experts to investigate a holistic approach to developing treatments urgently needed by the Parkinson's community that encompass neurology, immunology, microbiology and healthy lifestyle interventions.

The University of British Columbia Faculty of Medicine and the Pacific Parkinson's Research Centre (PPRC) thank the Pacific Parkinson's Research Institute (PPRI) for advancing our understanding of the role that the microbiome plays in the mechanisms of Parkinson's disease (PD) through its visionary support of the leadership of principal investigator Dr. Silke Appel-Cresswell, Associate Professor of Neurology and the Marg Meikle Professor in Parkinson's Research. Essential to advancing our understanding of PD, this research has great potential to allow innovation in shaping its progression.The UBC Faculty of Medicine, Dr. Appel-Cresswell and her team are pleased to prepare the following progress update.

A Personal Message from Dr. Appel-Cresswell

In the face of the considerable ongoing challenges presented by the COVID-19 pandemic, the Microbiome Analysis program has continued to blossom and create new opportunities for synergism and collaboration around the world. A highlight has been the publication of our groundbreaking study that suggests a strong correlation between the MIND and Mediterranean diets and later onset of PD. While we have long known that the MIND diet offers neuroprotective benefits for Alzheimer's patients, this is the first time we have shown that people with PD have a significantly later age of onset if their eating patterns closely align with a Mediterranean-type diet, which focuses on a reduced meat intake and greater focus on vegetables, fruits, whole grains and healthy fats. There is a lack of medications to prevent or delay PD, but we are optimistic that this new evidence suggests that nutrition could potentially delay the onset of the disease.

I am excited at what we may achieve over the coming years. Knowing that nutrition is a critical factor, we are eager to examine its impact on the related clinical mechanisms in the microbiome and the clinical course of PD. With your continuing support, we anticipate translating our newfound knowledge to build projects and communities, undertake robust research into lifestyle and microbiome interventions and connect patients and carers who otherwise may be isolated. Thank you!

Microbiome Studies

Dr. Appel-Cresswell and her collaborators are progressing in one of the largest and most extensive investigations of the relationship between PD and the gut microbiome - the billions of bacteria and other microorganisms that co-exist with other human cells in the lower intestine that helps with digestion, metabolism, immune function and brain health. Dr. Appel-Cresswell is collecting the longitudinal data needed to determine the delicate balance of the microbiome over time and how this relates to clinical symptoms of PD and biochemical and immune system markers.

The initial study of the role of the microbiome in PD (MB 1) ran from November 2016 to October 2019, with a follow-up study (MB 2) being conducted from September 2017 to September 2019. A third study encompassing a longitudinal study in PD, REM sleep behaviour disorder and a randomized, double-blind controlled trial of the effect of probiotics in PD-related depression (MB 3), funded with contributions from philanthropist Kurt Gagel, began in January 2018. Dr. Appel-Cresswell and her team have set up a clinical trials unit at the Pacific Parkinson's Research Centre and are collaborating with Winclove, the company providing the probiotic for use in the study, which has a projected completion date of February 2023. The overall goals of MB1, MB 2 and MB 3 are to:

- Analyze the microbiome and clinical data of N=300 participants at baseline and after a period of one year.
- Establish microbiome, immune system markers, metabolomics and genetics.
- Perform ongoing clinical follow-ups every year for up to five years
- Produce clinical data encompassing motor and non-motor functions, demographics and nutrition.

The current status of MB1, MB2 and MB3 are as follows:

	Recruitment October 2021	
PD Year One (baseline)	333, finalized	Papers published with more data analysis ongoing
PD Year Two follow up	208, finalized	Data analysis ongoing
PD Year Three follow up	183, finalized	Data analysis ongoing
PD Year Four follow up	119	Ongoing follow up
PD Year five follow up	51	Ongoing follow up
REM Sleep Behaviour Disorder	18 (of a target of 20)	Ongoing recruitment
Randomized placebo-controlled trial into probiotics in PD (ProD)	To start in spring 2022 with a recruitment goal of 50	Health Canada approval obtained, ethics submission in October 2021

Future Objectives

Dr. Appel-Cresswell's long-term objectives continue to be the development and optimization of treatments and preventive strategies for Parkinson's disease and related disorders with a focus on the role of the microbiome, nutrition, exercise and other lifestyle interventions, demonstrated by the visionary leadership that led her to create the BC Brain Wellness Program.

Thanks to PPRI's ongoing support of Dr. Appel-Cresswell's microbiome research through MB1, MB2 and MB3, her approaches to future research will include related observational and mechanistic studies, clinical trials and implementation studies.

Dr. Appel-Cresswell's milestones for the next five-year term as the Marg Meikle Professor include:

- The completion of the five-year longitudinal microbiome project funded by PPRI and the publication of at least one to two papers annually based on microbiome-related research.
- The completion of five clinical trials into nutrition and/or microbiome-based and combined lifestyle interventions (e.g. nutrition plus exercise plus mindfulness).

- The development of microbiome-based interventions, including fecal transplants and designer probiotics.
- Systematic testing of nutrition interventions in PD using randomized control trials.
- The creation of a nutrition-microbiome-brain health Research Cluster at UBC.
- Deepening of international collaborations on the theme of nutrition-microbiome-brain health and other lifestyle interventions for the prevention and treatment of PD and related disorders.
- The incorporation of lifestyle interventions into the standard clinical care for Parkinson's disease and other brain disorders, leveraging the impact of the BC Brain Wellness Program.

Dr. Appel-Cresswell has identified the need for biomarkers and intermediate markers implicated in the disease process (e.g. inflammatory markers) as a research priority to allow the assessments of clinical interventions and their impact on the disease process.

Funding and Collaboration Highlights

Future Objectives

PPRI's philanthropic leadership has been instrumental in enabling Dr. Appel-Cresswell to highlight the importance of her research and translate it to encouraging new areas of exploration for treatments and healthy lifestyle interventions for the PD community. Your continuing support has helped Dr. Appel-Cresswell leverage more than $600,000 in additional microbiome research funding and student support and open up collaborations with a variety of external sources, including the Weston Family Foundation, Parkinson Canada, Parkinson Society of British Columbia, and the Canadian Consortium on Neurodegeneration and Aging.

Current Collaborations

In addition to attracting financial support, Dr. Appel-Cresswell has created meaningful collaborations and found synergies to increase the effectiveness of her studies. They include support from Professor Brett Finlay's lab at UBC's Michael Smith Laboratories in sample analysis and fundamental lab-based research, the Borgland Family Brain Tissue and DNA Bank at the Djavad Mowafaghian Centre for Brain Health, which has provided technical support and sample storage and foundational support for a clinical trials program from the Pacific Parkinson's Research Centre.

Dr. Appel-Cresswell will continue to strengthen her national and international collaborations with researchers who are renowned in their fields as she advances her research and development of clinical trials with the goal to develop microbiome-based interventions for PD and its symptoms.

Collaborations at UBC

- Microbiology and Immunology: Dr. Brett Finlay
- Parkinson's Research Group PPRC: Drs. Jon Stoessl, Martin J. McKeown, Joseph K C. Tsui, Jason Valerio (also sleep clinic), Jonathan Squires, Tara Rastin, Melissa McKenzie
- Neuroscience/Inflammation, biomarkers: Drs. Cheryl Wellington, Brian MacVicar
- DMCBH Biobank: Dr. Seti Boroomand
- Huntington's: Dr. Blair Levitt
- Alzheimer's research: Dr. Robin Hsiung
- Multiple Sclerosis: Dr. Helen Tremlett
- Metabolomics/chemistry: Dr. Huan Tao
- Psychiatry: Drs. Fidel Vila-Rodriguez, Andrew Howard, Sophia Frangou
- Nutrition, Land and Food Systems: Drs. Yvonne Lamers, Tamara Cohen, David Kitts, Rickey Yada

National and International Collaborations

- University of Calgary: Drs. Davide Martino, Laura Sycuro, Kathy McCoy, Oury Monchi
- University of Ottawa: Drs. Michael Schlossmacher, Maxime Rousseaux
- McGill, Montreal: Drs. Ronald B. Postuma, Ziv Gan-Or
- University of Toronto: Dr. Howard Chertkow
- University of Malaya, Malaysia: Dr. Ai Huey Tan

Thank You

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The UBC Faculty of Medicine and the PPRC are deeply grateful to the PPRI for supporting our investigations into the role of the microbiome in the development of Parkinson's disease and the development of an integrated approach to new opportunities for wellbeing for patients and care partners.

Thank you for enabling our experts in neurology, microbiology, immunology, nutrition, exercise, metabolomics, psychiatry and other fields to proceed with this extensive research program to inform the development of much-needed treatments and interventions for Parkinson's disease.

Addendum

Peer-Reviewed Journal Publications

Microbiota Composition and Metabolism are Associated with Gut function in Parkinson's Disease: Cirstea MS, Yu AC, Golz E, Sundvick K, Kliger D, Radisavljevic N, Foulger LH, Mackenzie M, Huan T, Finlay BB, **Appel-Cresswell S.** Mov Disord. 2020 Jul;35(7):1208-1217. Epub 2020 May 1. PMID: 32357258.

At publication, this was the largest single-centre microbiome in PD paper published and among largest of all cohorts internationally. Published in March 2020 in Movement Disorders, this groundbreaking paper has been cited by 59 academic papers. It has an Altmetric Attention Score of 37, placing it in the top 5% of all research outputs (over 17 Million) scored, a high Attention Score compared to outputs of the same age (92nd percentile), a high Attention Score compared to outputs of the same age and source (94th percentile, #6 out of 92 outputs). These figures are retrieved from wiley.altmetric.com/details/81178275, accessed January 23, 2022.

The Gut Mycobiome in Parkinson's Disease: Cirstea M, Sundvick K, Golz E, Yu A, Boutin RCT, Kliger D, Finlay BB, **Appel-Cresswell S**. J Parkinsons Dis. 2020 Oct 31. doi: 10.3233/JPD-202237. Online ahead of print. PMID: 33164944. Press coverage see above.

MIND and Mediterranean Diets Associated with Later Onset of Parkinson's Disease: Metcalfe-Roach A, Yu AC, Golz E, Cirstea M, Sundvick K, Kliger D, Foulger LH, Mackenzie M, Finlay BB, **Appel-Cresswell S.** Mov Disord. 2021 Apr;36(4):977-984. doi: 10.1002/mds.28464. Epub 2021 Jan 6. PMID: 33404118.

Published in Movement Disorders, January 2021, this detailed study illustrated how adherence to healthy, Mediterranean-type eating patterns are associated with not only slowing the disease progression of Parkinson's but also linked to a reduced risk of developing PD and the symptoms of promodral PD. The study showed that in men, the age of onset could be delayed by up to eight years, and in women, up to seventeen years. It received and Altmetric Attention Score of 236, placing it in the 99th percentile for all research outputs scored, one of the highest-scoring outputs from this source (#13 of 4,244).

It also received a high attention score compared to outputs of the same age (99th percentile) and high Attention Score compared to outputs of the same age and source (99th percentile, #1 out of 118 outputs) by Altmetric (https://wiley.altmetric.com/details/97258054, accessed January 23, 2022).

Age-Matching in Pediatric Fecal Matter Transplants: MacLellan AD, Finlay BB, **Appel-Cresswell S**. Front Pediatr. 2021 Jul 16;9:603423. doi: 10.3389 / fped.2021.603423. PMID: 34336729.

Data-Driven Prediction of Fatigue in Parkinson's Disease Patients: Lee DG, Lindsay A, Yu A, Neilson S, Sundvick K, Golz E, Folger L, Mirian M*, **Appel-Cresswell S***. Accepted for publication by Frontiers Artificial Intelligence – Medicine and Public Health, August 2021. *Joint senior authors.

This study analyzed the clinical data collected with the Microbiome Project to optimize the recognition of fatigue in individuals with Parkinson's disease.

Gut Microbiome in Parkinson's Disease: New Insights from Meta-Analysis: Toh TS, BSc, Chong CW, Lim SY, Bowman J, Cirstea M, Lin CH, Chen CC, **Appel-Cresswell S**, Finlay BB, Tan AH. Parkinsonism Relat Disord. 2022 Jan;94:1-9. doi: 10.1016/j.parkreldis.2021.11.017. Epub 2021 Nov 17.. PMID: 34844021.

This study was an international collaboration between Malaysia, Canada, USA and Taiwan.

The Oral and Fecal Microbiota in a Canadian Cohort of Alzheimer's Disease: Cirstea M, Kliger D, MacLellan A, Yu AC, Langlois J, Fan M, Boroomand S, Kharazyan F, Hsiung R, MacVicar B, Chertkow H, Whitehead V, Finlay B*, **Appel-Cresswell S***. Accepted for publication in the Journal of Alzheimer's Disease, December 2021. *Joint senior authors.