Precision medicine in Parkinson's disease:
Past lessons and conquering new frontiers

26-27 January 2023

Luxembourg - Belval

Contents

Welcome message from Prof. Dr. Rejko Krüger

Dear Colleagues, dear Students, dear Friends,

it is a great pleasure for me to welcome you all to Luxembourg for our conference on "Precision Medicine in Parkinson's disease: past lessons and conquering new frontiers". This is the third of a series of scientific conferences organised by our trilateral network 'Luxembourg-German-Indian Alliance on Neurodegenerative diseases and Therapeutics (Lux-GIANT). This alliance was founded in 2014 and aims at performing trans-ethnic genomic studies in neurodegenerative diseases such as Parkinson disease (PD). Our 2023 conference was organized together with my colleagues from the Lux-GIANT consortium, Prof. Asha Kishore from the Sree Chitra Tirunal Institute for Medical Sciences and Technology (SCTIMST) in India, and PD Dr. Manu Sharma from the University of Tübingen in Germany and will represent the achievements of our Lux-GIANT consortium while broadening its scope to include the expertise of key international speakers. The conference will cover a broad range from clinical characterisation of large cohorts, genetic stratification, and dissection of molecular pathways of neurodegeneration that translate into novel mechanism-based therapies in PD. Our two days event brings together clinicians and researchers to discuss research breakthroughs in the area of stratification and treatment of PD and foster collaborations among the international experts. We will hold six dedicated and complementary sessions:

1) Cohorts and Clinical Phenotypes: illustrates the latest developments in clinical dissection of PD and discuss the harmonisation of efforts to create deeply phenotyped longitudinal cohorts multiscale data integration.
2) PD Genetics and genomics: presents the current advances in functional genomics and genetic dissection of the heterogenous group of PD patients.
3) PD and Cognition – from risk factors for dementia in PD to prevention: addresses newly identified risk factors for cognitive decline in PD.
4) Genetic stratification for precision medicine updates on the advances of Genome-Wide Association Studies to define novel loci and genetic burden.
5) From cellular mechanisms to novel biomarkers: focuses on the identification of molecular pathways implicated in the pathogenesis of PD defining new biomarkers.
6) Data management and bioinformatics analysis: tackles the challenges of data management in large cohorts and the development of a European hub for at risk cohorts.

I am looking forward to our conference and would like to invite you to a fruitful multidisciplinary and translational exchange among speakers and participants.

Best regards,
Rejko Krüger

Luxembourg City

Points of Interest and attractions

Luxembourg-City is a city that deserves to be known and visited throughout all the seasons. The most prominent attractions include the "casemates" or bunkers, which are among the longest subterranean tunnels in the world. The casemates that once formed an extraordinary network of 23 km were carved into the rocks of the city and are a top attraction in Luxembourg-City. Not only did they provide shelter for thousands of defenders with their equipment and horses, but they were also home to workshops of artillery and armaments, kitchens, bakeries, slaughterhouses, etc.

Luxembourg-City has a plethora of historic and tourist sites simply waiting to be discovered. Picturesque squares, quaint back alleys that make you feel alive, majestic boulevards and beautifully sculptured parks that coax you in for a stroll. The city of Luxembourg is proud of its eventful history that began over a thousand years ago. As the headquarters of important European institutions, Luxembourg is famous all over the world. Welcome to Luxembourg-City!

Luxembourg is proud to be the first country in the world to offer nationwide free public transport for everyone. Your travels have never been easier: just hop onto a bus, train or tram and you're good to go!

More information on the tourist office website: https://www.vdl.lu/

Venue

University of Luxembourg - Belval Campus
Maison du Savoir - 1 on the map
2, avenue de l'Université
L-4365 Esch-sur-Alzette
GPS: 49.504839 | 5.948214

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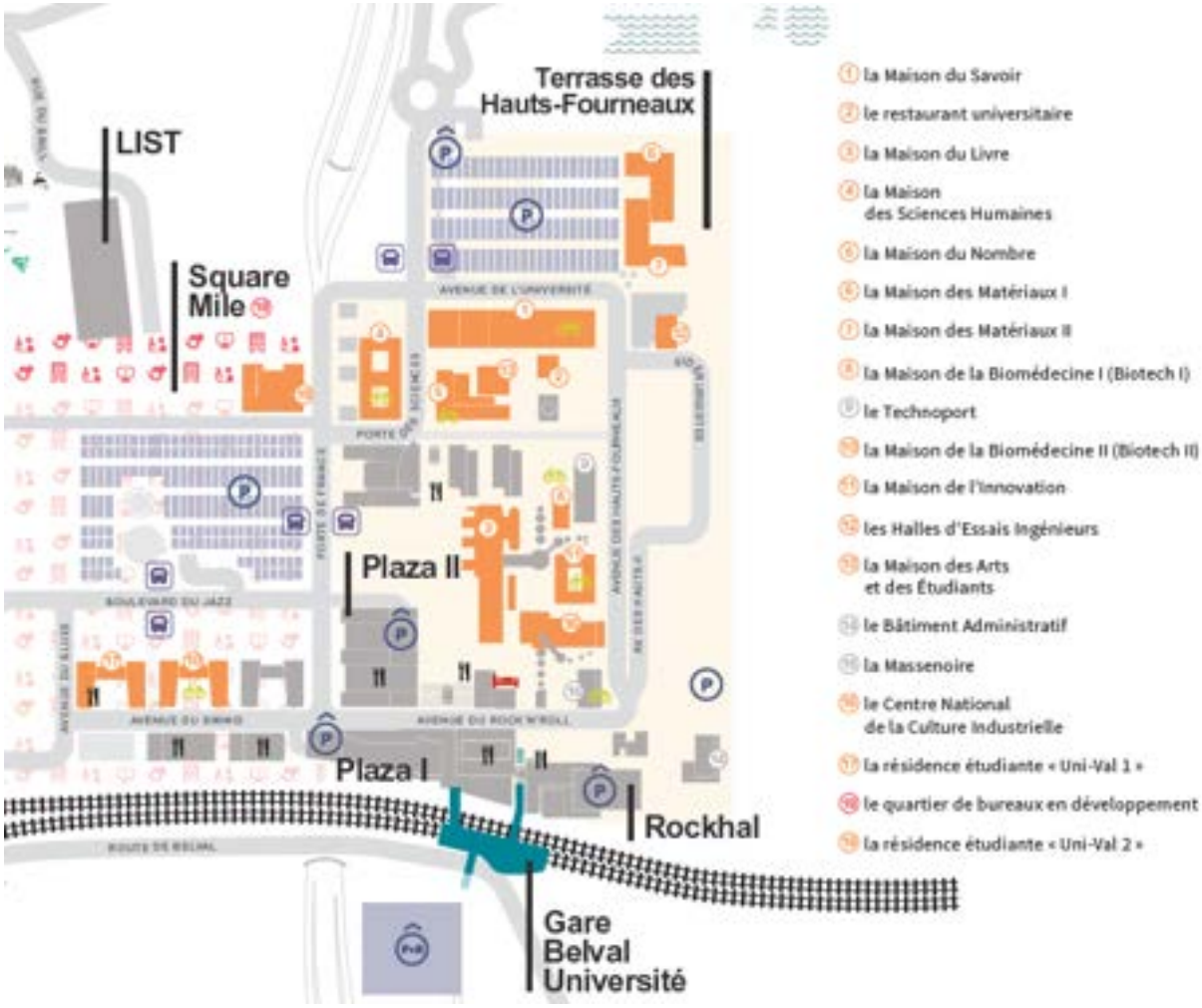
https://wwwen.uni.lu/contact/belval_campus



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http://sos.luxweb.lu/en

Organising Committee

Organising Committee


From left to right:
Prof. Dr. Rejko Krüger, Mrs. Bianca Dragomir

Scientific Advisory Board



From left to right:
Prof. Dr. Rejko Krüger, Prof. Asha Kishore, PD Dr. Manu Sharma

Sponsors

COFUNDING

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Supported by the International Parkinson and Movement Disorder Society

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Speakers

Veerle Baekelandt

Veerle Baekelandt, PhD, is a neurobiologist and full professor at the faculty of medicine of the KU Leuven, Belgium.
She heads the laboratory for Neurobiology and Gene Therapy. The general interest of the lab concerns the molecular pathogenesis of Parkinson's disease and related disorders. The approach consists of generating novel cellular and rodent models based on genes involved in familial forms of Parkinson's disease, with the aim to better reproduce the pathogenesis of the disease than the existing models. The final goal is to develop novel causal therapeutic strategies that can cure or slow down the disease. Her current research focuses on the role of α-synuclein aggregation in Parkinson's disease and multiple system atrophy, and on the function of LRRK2, a kinase linked to Parkinson's disease. The lab is using viral vector technology, stereotactic neurosurgery and non-invasive molecular imaging as core technologies. Dr. Baekelandt is recognized internationally for the application of viral vectors in rodent brain to model and study Parkinson's disease. She has also contributed to groundbreaking research demonstrating a prion-like behaviour of the α-synuclein protein.

Soraya Bardien

Soraya Bardien is a professor of human genetics at Stellenbosch University in Cape Town, South Africa. She did all her training at the University of Cape Town. During her studies, she undertook research training visits to Baylor College of Medicine in Houston, University of Texas Southwestern Medical Center in Dallas and the Institute of Ophthalmology in London.
She has done research on the genetic basis of several disorders over the years including retinitis pigmentosa, essential hypertension and diabetes. Her current research is focussed on investigating the genetic causes of Parkinson's disease (PD) in the diverse South African population. Her work has shown that South African individuals with PD typically do not have pathogenic variants in the known PD genes and therefore potentially harbour variants in novel PD genes.
Soraya served as the Chair of the Southern African Society for Human Genetics (2017-2019), and she currently serves on several international committees including the African Society of Human Genetics, GP2 Underrepresented Populations Working Group, Steering Committee of Genetic Epidemiology of Parkinson's Disease Consortium, and the International Parkinson and Movement Disorder Society's Task Force on Recommendations for Clinical Genetic Testing in Parkinson's Disease. She also serves on the Editorial Boards of Frontiers in Neurology, Parkinson's disease and Related Disorders and the Journal of Movement Disorders.

Soraya has won several awards, and was the second runner up for the Department of Science and Technology's South African Women in Science Award (2018) and a finalist for the National Science and Technology Forum-South32 Lifetime Award (2021). To date, she has co-authored 97 research publications, and three book chapters.
When she's not working, Soraya likes to spend time working in her garden, watching crime documentaries or hiking in the beautiful mountains in South Africa.

Rupam Borgohain

Dr. Rupam Borgohain, is a Retd. Professor of Neurology at Nizam's Institute of Medical Sciences (NIMS), Hyderabad, with an experience in neurology and especially movement disorders over two decades. Currently, he's working as a senior consultant neurologist at CNC hospital.
He is dedicated to the care of patients, with expertise in movement disorders especially dystonia, Parkinson's disease and mentorship of his students. He started the DBS programme in NIMS with more than 550 surgeries conducted under his stewardship since 2000.
He has also conducted numerous clinical trials, notable among them being Safinamide for Parkinson's disease, which he was the lead author and which received EMA clearance in 2014 and is under consideration by the FDA for marketing in USA recently.
He has established an Indian network of researchers in the field of Movement disorders (Parkinson's Research Alliance of India- PRAI) with Prof. Kapil D Sethi and Prof Madhuri Behari and is striving towards collaborative research.
He has published several papers in various national and international journals, has conducted multiple symposia, workshops, conferences and has delivered lectures and talks worldwide.

Kathrin Brockmann

Kathrin Brockmann, MD, serves as head of the largest outpatient clinic for parkinsonian syndromes at the University of Tuebingen in Southern Germany. Over 120 patients seen at the clinic every month undergo standardized clinical evaluation for the whole spectrum of motor and non-motor symptoms. As a group leader at the Hertie Institute for Neurodegenerative Diseases in Tuebingen, Dr. Brockmann conducts large-scale clinical studies to better understand the different phases of neurodegeneration as well as symptom development and progression to enable more effective, individualized therapies. In this context, dividing people with neurological diseases into groups based on results of genetic testing and also based on analysis of biofluid samples is much needed for the development of such therapies. Currently, Dr. Brockmann serves as a primary investigator in four large international and national research projects, including the Parkinson's Progression Markers Initiative (PPMI), The Michael J. Fox Foundation's landmark clinical study to find biomarkers — disease indicators that are critical missing

links in the search for better Parkinson's treatments. She is also involved in clinical trials of novel therapies. As clinical coordinator of the Neurobiobank Tuebingen, whose inventory exceeds 300 thousand biosamples, she conducts clinical research and studies biomarkers.

Jean-Christophe Corvol

Jean-Christophe Corvol is Professor of Neurology at Sorbonne Université, head of the Department of Neurology at the Pitié-Salpêtrière hospital, co-leader of the Molecular Pathophysiology of Parkinson's disease research team at the Paris Brain Institute (ICM), and co-chair of the French clinical research network for Parkinson's disease and movement disorders (NS-Park). JC Corvol has a training in both Neurology and Pharmacology (MD in 2003), has done a PhD (2005) in experimental neurosciences on dopamine signalling in the laboratory of JA Girault (Institut du fer à moulin, Paris) and a post-doc at UCSF in the neurogenetic laboratory of J. Oksenberg (San Francisco, USA). His fields of interest are molecular basis, genetic modifiers and pharmacology of Parkinson's disease. The approach is transversal, combining experimental models and genetic association studies in well-phenotyped cohorts. JC Corvol is leading a national cohort of Parkinson's disease patients in France for precision medicine and patients stratification. JC Corvol has published >250 papers in peer review journals (H index=65). He is member of the French societies for Neurology, Pharmacology and Neurosciences, past officer of the EU section of the International Movement Disorder Society, member of the scientific panel of the European Academy of Neurology, and member of the editorial board of the Movement Disorders journal.

Thomas Gasser

Thomas Gasser is a clinical neurologist and neuroscientist. He studied Medicine at the University of Freiburg, Germany, and at Yale University Medical School, New Haven, Connecticut. He trained as postdoctoral fellow at the Massachusetts General Hospital and Harvard Medical School in Boston. In 2002, he became Professor of Neurology and Director of the Department of Neurodegenerative Diseases and since 2008 he is chairman of the board of directors at the Hertie-Institute for Clinical Brain Research (HIH), University of Tübingen. Since 2013 he is also Coordinator for Clinical Research at the German Center for Neurodegenerative Diseases in Tübingen and since 2020 he serves as a vice-dean for research of the medical faculty.
His areas of research are the genetic and molecular basis of Parkinson's disease (PD), dystonias and other movement disorders, as well as their diagnosis and treatment.

Anne Grünewald

Prof. Anne Grünewald is the recipient of an ATTRACT career development grant from the Luxembourg National Research Fund (FNR) and Head of the Molecular and Functional Neurobiology Group at the LCSB, University of Luxembourg since 2016. Her research interest lies in the contribution of mitochondrial genome alterations to the pathogenesis of PD. Her team is specialized in mitochondrial function and mtDNA (single-cell) analysis techniques, which are applied to iPSC-derived neuronal and glia models. Among other involvements, Prof. Grünewald is a principal investigator in the Research Unit "ProtectMove" funded by the German Research Foundation and the FNR. She is also a (co-)principal investigator in the FNR-funded CORE projects CAMeSyn and RareCom as well as the doctoral training units I2TRON, CiTICS and PARK-QC at the University of Luxembourg. She has acquired >5 million EUR of grant support. Prof. Grünewald is a member of the Luxemburgish National Centre for Excellence in Research on Parkinson's Disease (NCER-PD) and served as scientific advisory board member for the Horizon 2020 project SysMedPD. She is a member of the University Council and the Gender Equality Committee of the University of Luxembourg as well as a steering committee member of the University of Luxembourg Leadership Academy (ULLA). In addition, she acts as ad-hoc reviewer for multiple foundations and journals and was invited to join the Editorial Board of Frontiers in Neurology and Cells.

Nobutaka Hattori

Prof. Nobutaka Hattori is a Chairman and Professor of the Department of Neurology, Juntendo University School of Medicine, Tokyo, Japan. Since 2020, he is the Team Leader, Neurodegenerative Disorders Collaborative Laboratory, RIKEN Center for Brain Science. He was involved in research about molecular mechanisms of Parkinson's disease (PD) since 1989. He found decrease in the amount of complex I in the substantia nigra of PD patients. More recently, his collaborators and he identified the disease gene for an autosomal recessive form of young onset familial PD, and named the gene as "parkin". This is the second form of familial PD in which the disease gene was identified. In addition, they found that the gene product, parkin was direct linked to ubiquitin- proteasome pathway as an ubiquitin ligase. This discovery suggested that protein degradation system was involved in the pathogenesis of not only monogenic form of PD but also sporadic PD. He has more than 500 peer-reviewed papers. Now he has been working hard for investigating and developing therapeutic methods not only for PD but other neurological diseases.

Asha Kishore

Dr Kishore is one of first fully trained Movement Disorder specialists in India and contributed substantially to establishing the subspecialty in the country. She graduated from Government Medical College, Thiruvananthapuram in 1984 with several gold medals and first rank in the University of Kerala, completed her MD in Internal Medicine from the same Institution in 1987 and DM (Neurology) from SCTIMSTin 1990. She then joined as academic faculty in SCTIMST and subsequently did two-year clinical research fellowship (1994-1996) in Movement Disorders in the University of British Columbia, Canada. She established the Comprehensive Care Center for Movement Disorders (CCCMD) at SCTIMST in 1997, the first of its kindin India and headed the same for 25 years since its inception. She has done sabbaticals in top Movement Disorder Programs in the University of Toronto, Canada, University of Pierre and Marie Curie, Paris and University College of London UK. She has been visiting faculty at University of Sydney and Hospital Sal Petriere Petite, Paris. Dr Kishore pioneered DBS program in India and the first DBS in India was done by the CCCMD of SCTIMST in 1999. She was trained in Microelectrode guided DBS from Grenoble University, France and Emory University USA. She is also lead Neurologist for R&D project aimed at indigenous development of low-cost DBS system, collaborating with Bhabha Atomic Research Center (BARC) and SCTIMST. She established the state- of- the- art Motor Physiology and Transcranial Magnetic Stimulation program and advanced Molecular Genetics Research lab in SCTIMST. She is currently heading the multicenter research team conducting the first Genome-wide Association Study of Parkinson's disease in India.

She started the first post-doctoral fellowship program in movement disorders in India and trained 12 post-doctoral fellows and also guided PhD students in areas related to Movement Disorders.She is an astute clinician, and teacher who has trained over 120 senior residents in Neurology and passionate researcher. Her areas of research interest include invasive and non-invasive brain stimulation in movement disorders and Genetics of movement disorders. She is very active international research collaboration with Dr Manu Sharma, University of Tubingen, Germany and Dr Sabine Meunier, University of Pierre and Marie Curie, Paris.

She has won several research grants from funding agencies including the Michael J Fox Foundation (USA), Inserm (France), ICMR and Department of Science and Technology, Govt. of India and has been member of several task forces, both national and international. Dr Kishore has several research publications to her credit, including publications in high impact international journals such as*Brain*, *Cerebral Cortex* and *Movement Disorders*. She has an H index of 30 and i10 index of 57. She has presented her research work at 34 International Parkinson's disease and Movement disorders and has been invited faculty at 13 international conferences. She is a member of the Scientific committee of the International Association of Parkinsonism and Related Disorders (Subsection of World Federation of Neurology), Member of the International consortium of researchers on the Genetic Epidemiology of Parkinson's disease (GEOPD), Founding member of the Movement Disorder Society of India and former member of the Executive Committee of the Asian Oceanian Section of International Parkinsons disease and

Movement Disorder Society. She is recipient of honours for outstanding contribution in the field of Health Care and Medical Proficiency and four Health Care Excellence awards.

Thomas Klockgether

Prof. Klockgether studied medicine at the University of Göttingen and during this time also carried out research at the Max Planck Institute for Experimental Medicine. After graduating, he went to Oldenburg for clinical training and then returned to the Max Planck Institute to work in basic research on Parkinson's disease. He completed his neurology training in Tübingen, where he also began to focus on degenerative ataxias, in addition to pursuing research on Parkinson's disease. In 1998, he was appointed as Professor and Chair of Neurology at the University of Bonn. Prof. Klockgether has been the Dean of the Medical Faculty of the University of Bonn from 2008 to 2011. Since February 2010 he has been Speaker of the Center for Rare Diseases Bonn (ZSEB) and since May 2011 Director of Clinical Research at the DZNE.

Jens Krüger

Jens Krüger leads the High Performance and Cloud Computing (HPCC) Group at the IT Center of the University of Tübingen operating Cloud and HPC infrastructure for various communities, including research data management.
He has a PhD in Chemistry and has broad experience in multiple biomedical research fields. He was holding basic and specialized lectures in bioinformatics and related fields. Currently he is Co-Spokesperson for the NFDI project DataPLANT coordinating the task area about Infrastructure, Software and Services. He is also part of the German Human Genome-Phenome Archive working on infrastructure and gateway. He is coordinating the Science Data Center BioDATEN, being responsible for multiple work packages. Further, he is speaker of the state-wide bwHPC Competence Center for Bioinformatics in Baden-Württemberg. Since 2016, he is member of the scientific advisory board of the Journal of Integrative Bioinformatics. Among other activities e.g. in EOSC-life, de.NBI/ELIXIR, graduate schools and CRCs, the recent focus lies on secure processing environments for the handling of sensitive biomedical data.

Anja Leist

Anja Leist is Associate Professor in Public Health and Ageing and Vice-Head of the Institute for Research on Socio-Economic Inequality at the University of Luxembourg. Her research focuses on cognitive ageing and dementia from a social and behavioural (risk reduction) perspective and is funded among others by the European Research Council. The five-year CRISP project investigates contextual-level influences on cognitive ageing and dementia with a focus on inequalities related to education, socioeconomic status, and gender. Jointly with Prof. Rejko Krüger and Prof. Paul Wilmes, she co-leads an interdisciplinary project on the links between the microbiome, socioeconomic status, and mild cognitive impairment, funded by the University of Luxembourg's Institute for Advanced Studies. Anja is elected Fellow of the Gerontological Society of America and co-founder of the non-profit organization World Young Leaders in Dementia a.s.b.l. (WYLD) network that facilitates careers of young professionals in dementia globally. She serves on the Scientific Advisory Board of the national dementia prevention programme pdp and regularly reviews for funders and journals. Her research has been published in Aging Research Reviews, International Journal for Equity in Health, Journals of Gerontology: Social Sciences, Gerontology, and Journal of Epidemiology and Community Health.

Patrick May

Dr. Patrick May is head of genome analysis group at LCSB. With his background in biology, computer science, and bioinformatics, having a PhD in theoretical biochemistry, he did his first postdoc at the Max-Planck-Institute for Plant Physiology in Potsdam, Germany. He started 2010 as an ISB fellow at LCSB working on whole genome sequencing projects in the Family Genomics group of Leroy Hood at the Institute for Systems Biology in Seattle, USA. He co-authored more than 150 journal publications in the fields of human genetics and genomics, microbiome, bioinformatics, and systems biology. His research is focused on human genomics and genetic of neurological and other diseases. He is leading or is part the genomic and genetic analysis teams for several national and international consortia and projects on PD and epilepsy, e.g., the Luxembourgish National Center for Excellence in Research on Parkinson's Disease, ProtectMove2, Epi25 and ILAE Genomics.

Brit Mollenhauer

Professor Brit Mollenhauer is a professor in the Department of Neurology at University Medical Center Göttingen and chief physician at Paracelsus-Elena-Clinic Kassel, both in Germany.
She has received her medical degree and completed her residency training in neurology at University Medical Center Göttingen. She was a research fellow in neurology at Harvard Medical School and Brigham and Women's Hospital, both in Boston, Massachusetts. At Harvard, she worked on developing biomarkers and studied α-synuclein as a biomarker in biological fluids.
Professor Mollenhauer serves on the executive steering committee of the Parkinson's Progression Markers Initiative (PPMI) of The Michael J. Fox Foundation for Parkinson's Research (MJFF) and is co-chair of the Biologics Working Group of PPMI. She is on the Therapeutic Evaluation Committee of the "Path-to-Prevention Initiative" of MJFF and co-chair of the Basic Science Special Interest Group of the Movement Disorder Society.
She has been a principal investigator for several phase 2 and 3 clinical trials. Her research is focused on the detection of biomarkers in human body fluids and development of experimental techniques to improve the diagnosis of movement disorders. She has published more than 125 scientific articles in journals such as *The Lancet Neurology, Neurology*, *Movement Disorders*, and *Brain* and received since 2019 every year an award as a highly cited researcher worldwide by Web of Science.

Pramod Pal

He is currently working as Professor & Head of Neurology at the National Institute of Mental Health & Neurosciences (NIMHANS), India, one of the largest tertiary neurology teaching centres in Asia. His core expertise and primary responsibilities include – patient care, teaching, and research, with additional responsibilities in hospital management. He has completed two Clinical Fellowship trainings: one in Movement Disorders at Vancouver, Canada, and the other in Neurology with emphasis on Electrophysiology in Movements disorders and Human Motor Physiology at Toronto, Canada. His basic degrees are MBBS, MD (General Medicine), Diplomate in General Medicine), and DM in Neurology from India. He has full and specialist registration in UK. He has expertise in managing common and rare movement disorders, neurodegenerative disorders, ataxias, dementias, patients with advanced Parkinson‟s disease and motor fluctuations, and those who have stereotactic operations (stimulation or ablation) for Parkinson‟s disease. He has more than 225 publications in National and International journals and books and is actively involved in several funded and non-funded research projects and auditing, especially in the field of Movement disorders-Parkinson‟s Disease, ataxias and genetics. He has also contributed extensively for the promotion of Movement Disorders in India and was the Founding Secretary of the Movement Disorders Society of India (MDSI) and now the founder Editor-in-Chief of the journal Annals of Movement

Disorders, which is the official journal of MDSI. He was also the Treasurer of Indian Academy of Neurology (IAN) and now the President-Elect of IAN. In the International field, a member of the Education Committees of the International Association of Parkinsonism and Related Disorders and the Asian and Oceanian subsection of International Parkinson and Movement Disorder Society (MDS-AOS) and a member of the Editorial Boards of Parkinsonism and Related Disorders and Movement Disorders Journal. Currently he is a member of the Rare Movement Disorders Study Group of IPMDS and Secretary- Elect for 2017-2019 and Secretary for 2019-2021 MDS-AOS.

Venkata Satagopam

Venkata Satagopam is a Senior Research Scientist and Deputy Head of Bioinformatics core facility, LCSB, University of Luxembourg; Technical Coordinator (TeC) of ELIXIR-Luxembourg Node and CTO & Co-founder ITTM S.A. Luxembourg. Before joining LCSB, between 2004-2012 he worked as a Senior Bioinformatics Scientist at the EMBL, Heidelberg. Before EMBL he worked as a Bioinformatics Scientist at LION bioscience AG, Heidelberg. He is having 20 year of working experience in various bioinformatics fields including Data Integration and Knowledge Management; Clinical and Translational Data Curation, Harmonisation, Integration and Analysis; Dynamic Visual Analytics; Text-mining; Deep learning and advanced machine learning technologies and has published 60 publications. He obtained his PhD from Technical University Munich (TUM), Munich, Germany in the field of Bioinformatics. He is an associate editor of Frontiers in Systems Biology, co-chair of ISCB Education Committee involved in the organisation of several conferences, workshops, code/data hackathons.

Jens Christian Schwamborn

In 2002 Jens obtained a diploma in Biochemistry from the University Witten/Herdecke in Germany and in 2005 a PhD in Biology from the University Muenster in Germany. He worked as a postdoctoral researcher at the Institute for Molecular Biotechnology in Vienna / Austria. Since 2013 Jens is head of the Developmental and Cellular Biology group at the Luxembourg Centre for Systems Biomedicine (LCSB) as well as Professor at the University of Luxembourg.
2019 Jens Co-founded OrganoTherapeutics SARL-S, where he currently acts as CEO. Before he was co-founder and CSO of Braingineering Technologies SARL (2016-2018).
The focus of his work over the last years was on Neurobiology, Stem Cell research and Parkinson's disease. In particular he is interested in using human induced pluripotent stem cells for the development of brain organoid and assembloid models, which are used for in vitro disease modeling.

Pankaj Seth

Dr. Seth's research endeavor after returning to India from National Institutes of Health, Bethesda, USA, has been originality of thinking, taking up challenges of direct relevance to national health problems – of neurodegeneration, particularly HIV-1, drug abuse, Zika virus mediated neuropathogenesis, and very recently effect of SARS-CoV2 on human brain.

The models developed by Dr. Seth are being used to understand molecular mechanisms of neurological deficits in HIV-1/AIDS patients, Parkinson's disease, Alzheimer's diseases and microcephaly in babies born due to Zika virus infections of mothers. These have been made available to various institutions such as IITs, IISc, AIIMS, JNU, NBRC, IGIB, BHU.

Recently, Dr. Seth started research to understand why COVID19 patients exhibit neurological symptoms as Brain Fog. Dr. Seth's laboratory is geared up to understand the cellular and molecular mechanisms as to how the SARS-CoV-2 affects the functioning of brain of COVID19 patients. His research has been highlighted twice by NATURE India and by the International Society of Neurovirology – based in USA, electronic and print media, reflecting its impact in the field.

Despite the fact that India has millions of HIV/AIDS patients, less than half a dozen researchers are engaged in studying molecular mechanism of neurocognitive and motor deficits (NeuroAIDS) in such patients, as it is challenging. Dr. Seth overcome these challenges with diligence, vision and scientific approach. He is among very few researchers working in the area of NeuroAIDS in India and also in the world. He was invited as collaborator by researchers from Johns Hopkins University, National Institute of Health, University of Nebraska and other prestigious institutions globally and within India. His research at NBRC has been extensively funded by NIH RO1, R21, Office of AIDS-NIH, U.S-India Bilateral Collaborative Research Partnerships (CRP) on the Prevention of HIV/AIDS and Co-morbidities, DST, DBT, ICMR.

The National Academy of Sciences India, National Academy of Medical Sciences and Indian Academy of Neurosciences (IAN) have elected him their Fellow. He has been appointed as area expert to number of DBT, ICMR task forces to lend his expertise. He also serves on Editorial boards of numerous international journals in various capacities.

Dr. Seth serves on the Board and Council of several international scientific bodies reflecting his research accomplishments and international visibility in the field. He is currently serving as Board member of International Society of Neuro Virology (ISNV), USA, International Council Member – Society of Neuro Immune Pharmacology (SNIP), USA and as Council member of Asia Pacific Society of Neurochemistry (APSN). He is promoting the cause of neuroscience in developing countries. Within India, he made significant contributions for promotion of neuroscience with his active role as General Secretary of IAN.

Andrew B. Singleton

Andrew received his B.Sc. from the University of Sunderland, UK, and his Ph.D. from the University of Newcastle upon Tyne, UK. His research initially focused on genetic determinants of dementia. After postdoctoral work at the Mayo Clinic, Andrew moved to the National Institute on Aging. He became a senior investigator there in 2007, and Laboratory Chief in 2008. In 2016 he became an NIH Distinguished Investigator. In 2021 Andrew became the Director of the new Center for Alzheimer's and Related Dementias (CARD) within the Intramural Research Program of the National Institutes of Health.

Andrew has published more than 700 articles. His group works on the genetic basis of neurological disorders including Parkinson's disease, Alzheimer's disease, dystonia, ataxia, dementia with Lewy bodies, and amyotrophic lateral sclerosis. The goal of this research is to identify genetic variability that causes or contributes to disease and to use this knowledge to understand the molecular processes underlying disease.

Andrew serves on several advisory and editorial boards. He has received the Annemarie Opprecht Award for Parkinson's disease research, the Jay van Andel Award for Outstanding Achievement in Parkinson's Disease Research, the American Academy of Neurology Movement Disorders Award, the Robert A Pritzker Prize for Leadership in Parkinson's Disease, and an Honorary Doctorate from the University of Sunderland.

Pille Taba

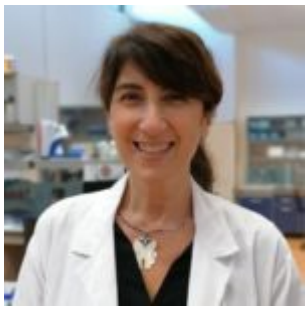
Professor Pille Taba is a Head of Department of Neurology and Neurosurgery and Head of Institute of Clinical Medicine of the University of Tartu, President of the Estonian Society of Neurologists and Neurosurgeons, and Head of the Neurology Commission for the Ministry of Social Affairs. She serves as a Chair of the European Section and a member of the International Executive Committee of the International Movement Disorders Society, a Co-Chair of the Panel on Movement Disorders of the European Academy of Neurology, and a member of the Scientific Advisory Group of Neurology of the European Medicines Agency.

Pille Taba was graduated from the University of Tartu, Estonia, and received her postgraduate medical training at the University of Vienna, the University College London, the Karlstad University Hospital, and the Minneapolis Clinic of Neurology. Her research interests have been focused on movement disorders including variable aspects of Parkinson's disease, toxic parkinsonism, and infections of the central nervous system. She has broad research contacts, among them collaboration with the University College London, University of Helsinki, and Uppsala University. Pille Taba has been an invited speaker at many international congresses and educational courses.

Caroline Tanner

Dr. Caroline Tanner has a clinical practice that specializes in movement disorders. Her research interests include the descriptive epidemiology, environmental and genetic determinants, biomarkers, early detection, nonmotor disease features and clinical trials for the secondary prevention, disease modification and symptomatic treatment of movement disorders. Her current research projects include conducting participant reported-outcomes, harnessing technology to increase participation in clinical research and access to care, the early identification of persons at risk of PD and the design and performance of trials to prevent PD. She leads the Fox Insight online study, and is a co-principal investigator of the Parkinson's Progression Markers Initiative study, the Trial of Parkinson's and Zolendronate (TOPAZ) study, the MICRO-PD study and studies of military service-related exposures and PD risk in Camp Lejeune and the Millennium Cohort. Dr. Tanner has been fortunate to mentor talented scientists from many countries, who themselves are now leading researchers and educators worldwide.

Enza Maria Valente



Enza Maria received her MD and residency in Neurology from the Catholic University in Rome and her Ph.D. from the University College of London. Upon returning to Italy, she established as an independent researcher at the Mendel Institute in Rome. She was appointed Associate Professor of Medical Genetics at the University of Messina and then Salerno, and finally moved to Pavia in 2017, where she took the positions of Full Professor of Medical Genetics at the University of Pavia and Head of the Neurogenetics Research Center and Genetic Diagnostic Lab at the IRCCS Mondino Foundation. One of her main research interests is the genetics of Parkinson Disease (PD) and movement disorders. In this field, she has largely contributed to gain knowledge on PINK1 with studies on its mutational spectrum and prevalenc, its phenotypic associations and its multiple molecular functions within neuronal cells. She has also been researching other PD genes, contributing to define the mutational and clinical spectrum of LRRK2, PARK2, SNCA and GBA in the Italian population. A second, relevant line of research focuses on the genetic basis of brain malformations, mainly of the cerebellum. Her research is funded nationally and internationally, including an ERC Starting Grant.
She is author of many scientific articles and reviews on international journals, and has been invited speaker at international congresses on genetics and movement disorders. She has been member of the Scientific Advisory Board of a PEARL research programme on PD genetics in Luxembourg, and is currently a member of the Scientific Committee and of the Monogenic Network of the Aligning Science Across Parkinson's Global Parkinson's Genetic Program (ASAP GP2). She has taken part in international projects on PD genetics, such as the FP7-funded MEFOPA study and the MJFF Global Genetics Consortium.

Peter-Jelle Visser

Pieter Jelle Visser, MD, PhD, is professor in molecular epidemiology of Alzheimer's disease at Maastricht University and Amsterdam University Medical Center in the Netherlands and is visiting professor at the Karolinska Institute in Stockholm, Sweden. His research focuses on the pathophysiology, diagnosis, prognosis and treatment of predementia Alzheimer's disease by combining different modalities such as imaging, proteomics, genetics and digital markers. He also coordinates projects that enable datasharing and data pooling in the AD field such as the Netherlands Consortium of Dementia Cohorts (NCDC), the Amyloid Biomarker Study (ABS), and the European Platform for Neurodegenerative Disorders (EPND).

Ullrich Wüllner

Prof. Dr. med. Ullrich Wüllner obtained a doctorate in medicine at the medial faculty Göttingen. Working at the Max Planck Institute for Experimental Medicine, was chosen as a fellow of the German National Academic Foundation (Studienstiftung), supported by a DFG grant trained as a reseach associate in neurology at the Massachusetts General Hospital (Harvard Medical School, Boston) and completed his specialist training at the Department of Neurology of Univ. Tübingen, where he was received the "venia legendi" in 1998 with a thesis on apoptotic cell death in neurodegenerative diseases. In Boston, he worked on the neurochemical anatomy of the basal ganglia, glutamate receptors and the role of excitatory neurotransmission in Parkinson's disease (PD). With Dr. Ole Isacson he positron emission tomography (PET) and high-field MRI techniques in primate models of PD PMID: 1515582, on molecular mechanisms of neuronal cell death (apoptosis, autophagy and necrosis in in vivo and in vitro models and on post-mortem tissue) and together with colleagues in chemistry, pharmacy and nuclear medicine, in particular Drs. Schmaljohann and Gündisch – he developed two PET tracers (PMID: 15959851, PMID: 16631078). In Bonn, he set up a research laboratory at the Department of Neurology in 1998 and continued the investigation of the molecular, cellular and pharmacological aspects of the pathogenesis of ataxias (SCA) and PD. In the Competence Network Parkinson e. V. the first German Parkinson gene bank was established in close cooperation with the German Parkinson (patient) Association (dPV) PMID: 17941852. Various projects in national and international research collaborations followed (eg DFG research group "SCA3" (FOR 427), BMBF Human Genome Project, Bonn (01GS0115) Subproject 9, BMBF project "Competence Network Parkinson" (01GI0401), EU Project "EuroSCA "(LSHM-CT-2004-503304), BMBF project" Brain Imaging Center West "(01GO0515), BMBF project" EPI-PD "(01KU1403D), EU project" Aetionomy "(FP7 / IMI / 115568) and several studies of drugs in phases 2 or 3: ECSPD98, E2007-E044-20, 248,595 proud phase IV, SP 873, CENA713DDE15, CENA713B2315, SP 882, S187.3.004,

P07-02, BF2.649, AX200–101). He is currently head of the Department of Movement Disorders and comm. Director and Chair of the Clinic for Neurodegeneration at the Department of Neurology, Prof. of the Medical Faculty of the Rheinische Friedrich-Wilhelms University Bonn and group leader at the German Center for Neurodegenerative Diseases (DZNE, Biomarker Parkinson). Recent projects focused on epigenetics PMID: 27120258 and the microbiome PMID: 28449715 in PD. In a translational clinical project, he leads a team of neurologists, neurosurgeons and radiologists using a system for Magnetic Resonance Imaging (MR) -focused focused ultrasound (MRgFUS), a newly developed procedure for interventional neuromodulation for targeted and minimally invasive treatment of tremor PMID: 30406441.

Agenda

Programme Precision Medicine in Parkinson's disease Thursday, 26th January (Day 1)	
9.00-10.00	Registration & Welcome coffee
10.00-10.15	Welcome address by Prof. Dr. Ulf Nehrbass, CEO of Luxembourg Institute of Health, and the organizers
	Introduction to Keynote Speaker by Dr. Manu Sharma
10.15-11.00	Keynote 1: Prof. Veerle Baekelandt, KU Leuven, BE *Unraveling the role of alpha-synuclein aggregation in Parkinson's disease and related disorders*
Session 1: Cohorts and Clinical Phenotypes Chair: Dr. Brit Mollenhauer	
11.00-11:20	Prof. Asha Kishore, Medcity, Kochi, IN. *Clinical and environmental risk factors of PD: interim observations of GAP-India*
11.20-11.40	Prof. Thomas Gasser, Hertie-Institute for Clinical Brain Research University of Tübingen, GER. *Genetic risk and resilience in Parkinson's disease*
11.40-12.00	Prof. Jean-Christophe Corvol, Paris Brain Institute, FR. *The value of nation-wide patient cohorts for impact for clinical care*
12.00-12.30	Funding agencies flash presentation: • Dr. Anna Naito, Associate Vice President, Research at Parkinson's Foundation. *PD GENEration: Providing Clinical Genetic Testing and Counseling for people with PD in North America.* Via Webinar • Dr. Sean Sapcariu, FNR Presentation: *The Luxembourg research ecosystem and funding opportunities*
12.30-13.30	Walking lunch with exhibition and poster session

Session 2: PD Genetics and genomics Chair: Prof. Asha Kishore	
13.30-13.50	Prof. Enza Maria Valente, University of Pavia, IT. *Understanding the mitochondrial phenotype of PD and its impact for precision medicine*
13.50-14.10	Prof. Soraya Bardien, Stellenbosch University, SA. *Genetics of PD in Sub-Saharan Africa: What do we know?*
14.10-14.30	Dr. Patrick May, LCSB, University of Luxembourg, LU. *Genetic risk prediction in PD*
14.30-14.45	Young scientist presentation: Dr. Kanchana Soman Pillai, Aster Medicty, IN. *Novel mutations in GRN, SQSTM1 and ADH1C —A case series of familial dementia with parkinsonism*
Session 3: Parkinson's disease and Cognition – from risk factors to prevention Chair: Prof. Dr. Ullrich Wüllner	
14.45-15.05	Prof. Pille Taba, University of Tartu, ES. *Parkinson's disease and Cognition – from risk factors to prevention*
15.05-15.25	Prof. Anja Leist, University of Luxembourg, LU. *Modifiable risk factors in dementia prevention*
15.25-15.45	Prof. Andrew Singleton, National Institute on Aging, USA. *Dissecting PD genetics worldwide – the GP2 initiative.* Via Webinar
15.45-16.00	Young scientist presentation: Dr Sahil Mehta, PGIMER, IN. *Comparison of cognitive, affective and autonomic functions in Parkinson's Disease patients with and without freezing of gait and its correlation with PET/CT*
16.00-16.30	Coffee break with exhibition and poster session
Session 4: Genetic stratification for precision medicine Chair: Prof. Dr. Thomas Klockgether	
16.30-16.50	Prof. Pramod Pal, National Institute of Mental Health and Neurosciences, IN. *Impulse Control Disorders in PD*
16.50-17.10	Prof. Rupam Borgohain, Nizam's Institute of Medical Sciences, IN. *Deep Brain Stimulation in India*
17.10-17.30	Dr. Kathrin Brockmann, University Tübingen, GER. *Lessons learned from GBA stratification for treatment and prediction*
17.30-17.45	Dr. Peter-Jelle Visser, Maastricht University, NL. *Molecular subtypes in Alzheimer's disease: relevance for Parkinson's disease*
17.45-18.00	Wrap up
18.00	**DRINKS RECEPTION**

Friday, 27th January (Day 2)	
8.30-8.45	*Welcome coffee*
8.45-9.00	Welcome address by Prof. Dr. Michael Heneka, Director of LCSB
	Introduction to Keynote Speaker by Prof. Dr. Nico J. Diederich
9.00-9.45	Keynote 2: Prof. Dr. Caroline Tanner, University of California San Francisco, USA. *Epidemiology, Targeting Parkinson's Disease Prevention: from Population Studies to Precision Medicine*
Session 5: From cellular mechanisms to novel biomarkers Chair: Prof. Dr. Jens Christian Schwamborn	
9.45-10.05	Dr. Brit Mollenhauer, Paracelsus-Elena Klinik, GER. *Toward biomarkers for prevention trials in Parkinson's disease*
10.05-10.25	Prof. Pankaj Seth, National Brain Research Center Manesar, IN. *A primary cell culture model of human brain cells for understanding neurodegenerative diseases.* Via Webinar
10.25-10.45	Prof. Anne Grünewald, LCSB, University Luxembourg, LU. *Cellular models for PD*
10.45-11.00	Young scientist presentation: Dr. Indrani Datta, National Institute of Mental Health and Neurosciences, IN. *Impairment in SHH responsiveness of iPSC derived neural progenitors carrying the LRRK2 I1371V mutation contributes to the ontogenic origin of lower dopaminergic-neuron yield*.
11.00-11.20	Coffee break with exhibition and poster session
	Introduction to Keynote Speaker by Prof. Dr. Rejko Krüger
11.20-12.05	Keynote 3: Prof. Nobutaka Hattori, Juntendo University, Japan. *"Importance of Biomarkers in Sinucleinopathies and Their Applications"*
Session 6: Data Management and Bioinformatics Analysis Chair: Dr. Reinhard Schneider	
12.05-12.25	Dr. Jens Krüger, University Tübingen, GER. *Research Data Management for sensitive data*
12.25-12.45	Dr. Venkata Satagopam, LCSB, University Luxembourg, LU. *Developing an EU hub for at risk cohorts*
12.45-13.00	Young scientist presentation: Gianfranco Frigerio, LCSB, University Luxembourg, LU. *A Methodology to perform accurate systematic-review with meta-analyses in Epidemiology: a case study for the Early-Life Exposure to Perfluoroalkyl Substances and its associations with Childhood Overweight and/or Obesity*
13.00-13.30	Funding agencies flash presentation DFG, MJFF & ICMR/DBT/DST
13.30-14.30	Walking Lunch
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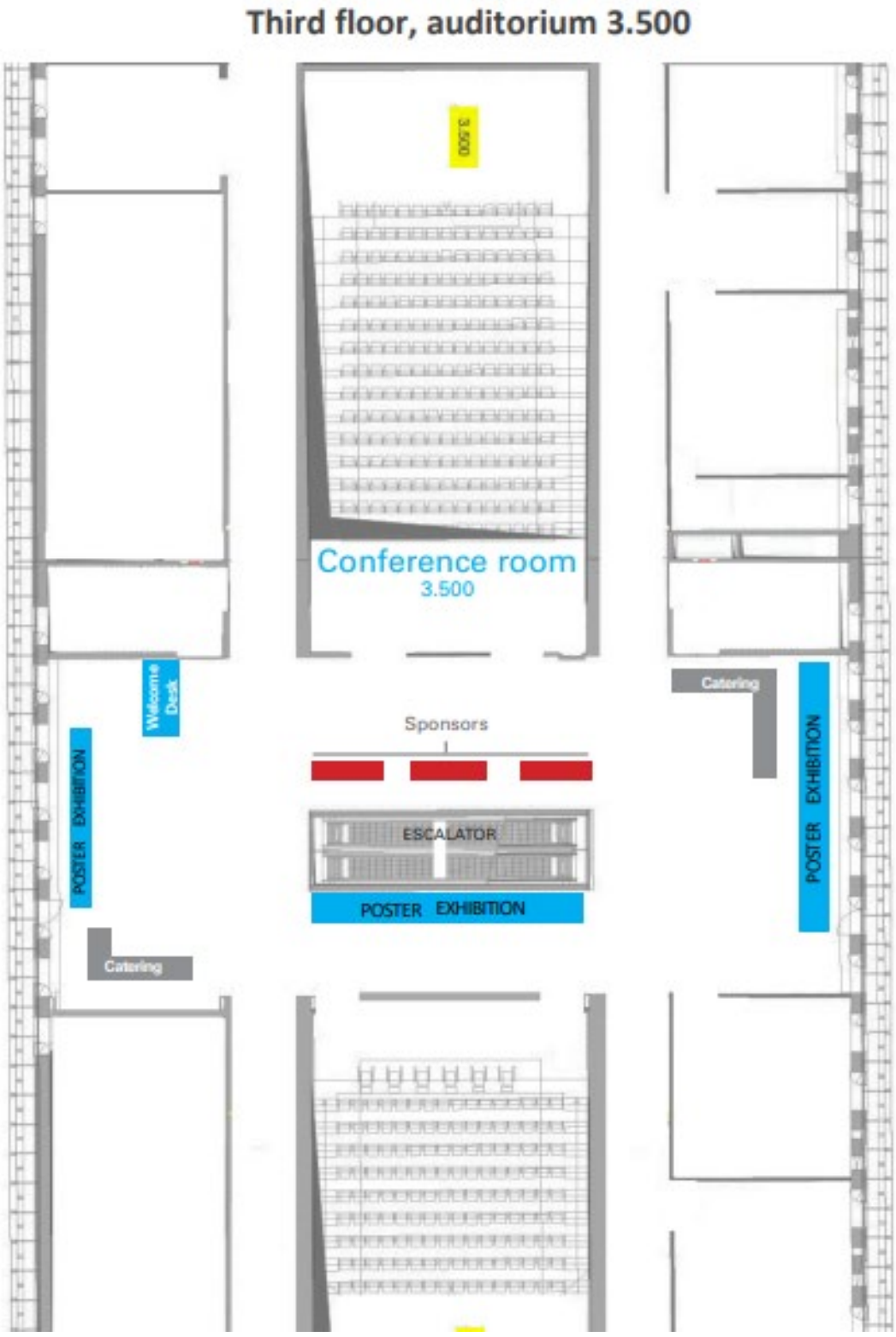
Auditorium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Poster Abstracts

Posters are displayed on Thursday 26 and Friday 27 in the coffee break areas.
The numbers below are indicated on the panels.

N	TITLE	N	TITLE
1	Genetic of Parkinson's disease in a cohort of Sudanese families	12	Analysis of insulin resistance as a risk factor for Parkinson's disease
2	Accurate long-read sequencing identified GBA variants as a major risk factor for parkinsonism in the Luxembourgish cohort	13	Validation and assessment of predictive ability for a polygenic score on Parkinson's disease
3	Long non-coding RNAs as neuroprotective targets in Parkinson's disease	14	Modelling digenic Parkinson's disease in a stem cell model carrying mutant N370s in the GBA1 gene and the homozygous deletion of exon 3 of PARK2
4	Structural variant analysis using long-read sequencing	15	Comparing multi-omics data analysis approaches on the metabolic and miRNA expression data from NCER-PD study
5	Improving blood transcriptomic studies by simplifying its library preparation	16	Parkinson's disease-associated mutation in MIRO1 leads to mitochondrial impairments and dopaminergic neuron degeneration
6	Genetic polymorphism and dopamine receptor related protein-based biomarkers in Parkinson's disease psychosis: a meta-analysis	17	Identification of Parkinson's disease-associated regulatory variants in neuronal and non-neuronal cell types
7	Elucidating microglia programs under PARK7/DJ-1-deficiency, a genetic cause of Parkinson's disease	18	Development of small molecule compounds targeting altered autophagy in Parkinson's disease specific microglia
8	The relationship between Paraoxonase 1 (PON1) gene polymorphism and Parkinson's disease risk in the North Indian population	19	Characterizing the role of Brain Renin Angiotensin system in the pathophysiology of neurodegenerative diseases
9	Genome wide association for Afrabia Parkinson's patients: how far have we come?	20	Functional validation of a mitochondria-specific polygenic risk score in patient-based models for stratification of idiopathic Parkinson's disease
10	Identification and functional characterization of VPS41 as a potential genetic modifier of penetrance in PG2019s LRRK2-associated Parkinson's disease	21	Engineering midbrain-specific assembloids with microglia for advanced disease modelling
11	Data-driven subtypes of Parkinson's disease using machine learning in Luxembourg Parkinson study	22	Alterations in neuron-derived exosomal cargo in Parkinson disease

N	TITLE	N	TITLE
23	Analyzing the metabolic function of DJ-1 in astrocytes to define its role in the pathogenesis of Parkinson's disease (PD) and glioblastoma multiforme (GBM)	**37**	Cognitive profile in prodromal Parkinson's disease
24	Parylation of α-synuclein oligomers in Parkinson's disease patients: a trigger for protein aggregation	**34**	Why is there often a "fight or flight" behavior in REM sleep behavior disorder?
25	SARS-CoV-2 induces dopaminergic neuron loss in midbrain organoids	**35**	Are pathogenic GBA mutations associated with a decline in patient-reported functional mobility?
26	Phenotypic profiling of human stem cell-derived dopaminergic neurons for drug screening applications	**36**	Cognitive profile in Parkinson's disease patients carrying glucocerebrosidase mutations
27	PINK1-pd neurons display altered tyrosine hydroxylase phosphorylation	**38**	Insights into the implementation of a nation-wide dementia Prevention Programme (pdp) in Luxembourg
28	MIRO1 retention at depolarized mitochondria in Parkinson's disease	**39**	More smoke than fire no speeding up of Parkinson's disease after covid-10 lockdown
29	Alpha-synuclein oligomers in skin biopsy: a reliable biomarker in idiopathic and GBA-associated Parkinson's disease	**40**	Visual dysfunction in Parkinson's disease GBA carriers: an exploratory analysis
30	Investigating the role of DJ-1/PARK7 in the immunopathogenesis of Parkinson's disease	**41**	Is it all about subjective cognitive complaint? A preliminary analysis in a Luxembourgish Parkinson's disease cohort
31	An in vitro and in vivo study of the impact of the Parkinson's disease-associated R272Q MIRO1 variant	**42**	Strategy to investigate the progression of cognitive decline in the longitudinal Luxembourg Parkinson's study
32	PARK7/DJ-1 regulates immunoageing in T-cell compartments	**43**	Development of an evaluation framework for digitally enabled integrated care: connected care PD
33	Gait parameters from instrumented time-up-and-go in Parkinson patients depend on GBA mutation	**44**	The neuropsychological profile and other clinical characteristics in non-affected GBA-carriers versus healthy non-carriers
		45	Education as a risk factor for mild cognitive impairment – the role of the gut microbiome

GENETIC OF PARKINSON'S DISEASE IN A COHORT OF SUDANESE FAMILIES

Yousuf Bakhit [1,2,3*], Sudan Parkinson's disease study group [3], Ahlam Hamed [4] Inaam N. Mohamed [4], Sarah M El-Sadig [4]. Maha A. Elseed [4], Christelle Tesson [5], Etedal Ahmed A. Ibrahim[6], Farouk Yassen Omer [7], Liena E. O. Elsayed [4], Haydar El Hadi Babikir [8]. Elfateh Abd-Allah Bukhari [9], Suzanne Lesage [5], Osheik Seidi [4], Jean-Christophe Corvol [5], Ullrich Wüllner [1,10*]

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9) Department of Neurology, Bashaier University hospital, and Khartoum Teaching hospital. Department of Medicine, Faculty of Medicine, Al-Neelain University, Khartoum Sudan
10) German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany

Abstract: In Africa, knowledge about the genetics underlying Parkinson Disease is scant. Few studies have been carried out, mostly limited by sample size, the studied variants or the methodology employed. *LRRK2* variants were associated with PD - in both autosomal dominant and sporadic forms whereas variants in *PINK1* were associated with early-onset PD. The population of the Sub-Saharan Africa region has been even less studied. Here, we present the first cohort of Parkinson's disease in a cohort of Sudanese families where we clinically assessed the patients according to the UK Brain Bank diagnostic criteria followed with MDS-UPDRS. Saliva samples were collected from 125 individuals (66 patients, 59 controls) for DNA extraction ((mean age of onset: 40.6 ±22.4 years). We used Twist custom panel, which allows screening of 34 genes, 27 risk variants and 8 candidate genes, which are mostly associated with Parkinsonism, and for negative families we performed whole exome sequencing, utilizing a Twist target enrichment protocol to develop the DNA library on Illumina NGS system. We found recurrent homozygous variant in PINK1 and compound heterozygous variant in PLA2G6, novel homozygous and compound heterozygous variants in PINK1, PLA2G6, PARK2, SYNJ1, DMXL2 and FIG4, and novel variants in candidate genes which where recurrent in multiple families, and the genes where reported to be associated with other neurological conditions. The intra-familial and interfamilial heterogeneity of PD families, even when associated with the same gene, are reflective of on of the highest genetic diversities in the world in addition to one of the highest consanguinity rates, which would account for possible founder effects and novel findings in health and disease.

Note: This is an ongoing project, which is part of the final stage of YB PhD.

Precision Medicine in Parkinson's disease:
Past lessons and conquering new frontiers
26-27 January 2023

ACCURATE LONG-READ SEQUENCING IDENTIFIED GBA VARIANTS AS A MAJOR RISK FACTOR FOR PARKINSONISM IN THE LUXEMBOURGISH COHORT

Sinthuja Pachchek Peiris[1], Zied Landoulsi[1], Lukas Pavelka[2,5], Claudia Schulte[3],Elena Buena-Atienza[4], Caspar Gross[4], Ann-Kathrin Hauser[3], Dheeraj Reddy Bobbili[1], Nicolas Casadei[4], Patrick May[1,*], and Rejko Krüger[1,2,5,*] on behalf of the NCER-PD Consortium

[1]LCSB, Luxembourg Centre for Systems Biomedicine, University of Luxembourg, Esch-Sur-Alzette, Luxembourg.
[2] Parkinson Research Clinic, Centre Hospitalier de Luxembourg (CHL), Luxembourg.
[3]Department of Neurodegeneration, Center of Neurology, Hertie Institute for Clinical Brain Research, German Center for Neurodegenerative Diseases, University of Tübingen, Tübingen, Germany.
[4]Institute of Medical Genetics and Applied Genomics, University of Tübingen, Tübingen, Germany; NGS Competence Center Tübingen (NCCT), University of Tübingen, Tübingen, Germany.
[5]Transversal Translational Medicine, Luxembourg Institute of Health (LIH), Strassen, Luxembourg.

**corresponding authors*

Objective: To assess the entire coding region of the glucocerebrosidase (*GBA*) gene for variants by long-read sequencing in the Luxembourg Parkinson's study and comprehensively characterize genotype-phenotype associations of Parkinson's disease (PD) patients carrying known and novel *GBA* variants.

Background: Heterozygous variants in the *GBA* gene are an increasingly recognized risk factor for PD. Due to the pseudogene *GBAP1* that shares 96% sequence homology with the *GBA* coding region, accurate variant calling by array-based or short-read sequencing methods remains a major challenge in understanding the genetic landscape of *GBA*-related PD.

Methods: We used a novel long-read sequencing technology to establish an assay for assessing the full length of the *GBA* gene. We used subsequent regression models (linear and logistic) for genotype-phenotype analyses.

Results: We sequenced 752 patients with parkinsonism and 806 healthy controls of the Luxembourg Parkinson's study. All *GBA* variants identified showed a 100% true positive rate by Sanger validation. We found 10.6% of PD patients carrying pathogenic *GBA* variants (severe, mild and low-risk). The risk variant, p.E365K, was the most common variant (3.5%) among PD patients. Eleven variants of unknown significance were identified of which three were not previously reported. We confirmed that severe *GBA* variants are associated with a more severe clinical phenotype in PD.

Conclusions: We established a novel, highly accurate method for targeted GBA gene sequencing to assess known and to find novel *GBA* variants. Furthermore, our study describes the full landscape of *GBA*-related parkinsonism in Luxembourg, showing a high prevalence of *GBA* variants as the major genetic risk in PD. Our approach provides an important advancement for highly accurate *GBA* variant calling, which is essential for providing access to emerging causative therapies for GBA carriers in the future.

LONG NON-CODING RNAS AS NEUROPROTECTIVE TARGETS IN PARKINSON'S DISEASE

Shubhra Acharya[1,2], Andrew I. Lumley[1], Lu Zhang[1], Semra Smajic[3], Jochen Ohnmacht[3,4], Anne Grünewald[3,5], Lasse Sinkkonen[4], Yvan Devaux[1], NCER-PD consortium

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3) Luxembourg Centre for Systems Biomedicine, University of Luxembourg, L-4362 Esch-sur Alzette, Luxembourg.
4) Department of Life Science and Medicine (DLSM), University of Luxembourg, 4367 Belvaux, Luxembourg.
5) Institute of Neurogenetics, University of Lübeck, D-23562 Lübeck, Germany.
6) Immuno-Pharmacology and Interactomics, Luxembourg Institute of Health, Luxembourg

Background
Long non-coding RNAs (lncRNAs) are implicated in several diseases including Parkinson's disease (PD) (1). Despite advances, novel biomarkers for PD diagnosis are in dire need. LncRNAs can regulate gene expression at transcriptional and post-transcriptional levels. They are tissue-specific and can be measured in various bodily fluids, which highlights their suitability as potential biomarkers. The use of lncRNAs as biomarkers in PD needs further investigation.
Aim
Our study aims to discover the role of novel lncRNAs in PD and to study their biomarker potential.
Methodology
Publicly available RNA sequencing data from PD patients and non-PD controls induced pluripotent stem cell (iPSC)-derived neurons and single cell RNA sequencing data from post-mortem midbrain tissues were re-analysed to identify novel lncRNAs. Differentially expressed lncRNAs were studied via quantitative PCR (qPCR) in the neuroblastoma cell line SH-SY5Y treated with 1-methyl-4-phenylpyridinium (MPP) to mimic mitochondrial dysfunction typically seen in PD. One of the most promising candidates was selected and further studied to uncover its role in PD. To this end, RNA pull-down, cell type-specific expression and over-expression experiments were performed. Moreover, the biomarker potential of this lncRNA was assessed via qPCR in 319 non-PD and 319 idiopathic PD (iPD) whole blood samples from the NCER-PD cohort (2).
Results
Analysis of publicly available RNA sequencing data revealed that 28 lncRNAs were differentially expressed in iPSC-derived neurons obtained from PD patients compared to those from non-PD controls (FDR <0.05). Of the top 10 differentially expressed (DE) lncRNAs, the expression of 1 lncRNA was downregulated; 4 were upregulated and the remaining five were not regulated in MPP treated SH-SY5Y cells. RNA pull-down of one of the top 10 DE lncRNA candidates, named lncG1, was found to interact with messenger RNAs coding for genes involved in PD development: tyrosine hydroxylase (TH) and alpha synuclein. Single-nuclei RNA sequencing of postmortem brain tissue and expression quantification in TH-positive iPSC-derived neurons showed lncG1 expression was specific to neurons in the midbrain and was found to be exclusively expressed in TH-positive dopaminergic neurons. Overexpression of lncG1 significantly increased TH and dopa-decarboxylase protein expression in SH-SY5Y cells treated with MPP as measured by Western blotting. Furthermore, ELISA results indicated a significant increase of dopamine in MPP-treated SH-SY5Y cells following lncG1 overexpression. Lastly, lncG1 expression was found to be significantly downregulated in whole blood samples from iPD patients compared to non-PD controls (both groups n=319, p=0.002).

Conclusion

Our study sheds light on the role of lncRNAs in PD. The expression of lncG1 was decreased in SH-SY5Y cells treated with MPP and in human iPD whole blood patient samples. LncG1 could significantly increase the expression of enzymes involved in the dopamine synthesis pathway, suggesting a neuroprotective role in PD. Further work is needed to validate the therapeutic and biomarker potential of lncG1.

References

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2) Hipp, G., Vaillant, M., Diederich, N. J., Roomp, K., Satagopam, V. P., Banda, P., Sandt, E., Mommaerts, K., Schmitz, S. K., Longhino, L., Schweicher, A., Hanff, A. M., Nicolai, B., Kolber, P., Reiter, D., Pavelka, L., Binck, S., Pauly, C., Geffers, L., Betsou, F., … Krüger, R. (2018). The Luxembourg Parkinson's Study: A Comprehensive Approach for Stratification and Early Diagnosis. Frontiers in aging neuroscience, 10, p 326. https://doi.org/10.3389/fnagi.2018.00326

STRUCTURAL VARIANT ANALYSIS USING LONG-READ SEQUENCING

Elena Buena-Atienza 1,2, Caspar Groß 1,2, Tobias Haack 1, Stephan Ossowski 1,2, Olaf Riess 1,2, Nicolas Casadei 1,2

1) Institute of Medical Genetics and Applied Genomics, University of Tübingen,
2) NGS Competence Center Tübingen, Tübingen, Germany

Most genetic analyses are currently being performed on genotyping arrays and next generation sequencing platforms. Both platforms provide robust information on single nucleotide polymorphisms, copy number variants and small insertions and deletions. However, both methods offer limited resolution of more complex structural variants such as inversion or translocation. We propose to use long-read sequencing to resolve in unsolved genomic cases potential structural variation suggested by whole genome sequencing. This poster focuses on the experimental design, the methodology and a few selected examples of this strategy.

IMPROVING BLOOD TRANSCRIPTOMIC STUDIES BY SIMPLIFYING ITS LIBRARY PREPARATION

Michaela Pogoda 1,2, Jakob Admard 1,2, Caspar Groß 1,2, Jeannette Huebener1, Olaf Riess 1,2, Nicolas Casadei 1,2
1) Institute of Medical Genetics and Applied Genomics, University of Tübingen,
2) NGS Competence Center Tübingen, Tübingen, Germany

Blood transcriptomics continuously gained popularity as it allows searching for potential disease biomarkers, study effect of genomic variants located in splicing relevant regions of genes, and validation of effect of deletion in non-coding regions of the genome. For many genomic facilities, depletion of ribosomal and immunoglobulin transcript is a convenient method to prepare RNA for next generation sequencing, as it allows the preparation of degraded RNA and homogeneous content of messenger RNA. We compared this strategy to the enrichment of polyA RNA. Our results show that depletion techniques lead to an over-representation of intron retention and to the depletion of immunoglobulin, which are of particular interest in multiple studies.

GENETIC POLYMORPHISM AND DOPAMINE RECEPTOR RELATED PROTEIN-BASED BIOMARKERS IN PARKINSON'S DISEASE PSYCHOSIS: A META-ANALYSIS

Pratibha Sharma, Rajinder K Dhamija
Institute of Human Behaviour and Allied Sciences, Dilshad Garden, New Delhi, India

Background: Precision medicine in Parkinson's disease (PD) having the drugs tailored to each PD patient holds immense potential. Dopaminergic pharmacotherapy is largely being used for treatment of PD patients. But the prolonged use of dopaminergic medications for treating motor symptoms in PD, results in complications such as PD psychosis (PDP) in nearly half of these patients. PDP is manifested through formed hallucinations, illusions and delusions, while the mechanism for this is completely unknown. Absence of any lab test hampers the pharmacotherapy of PDP. Genetic variants in dopamine pathway related genes can be determined to test as marker of susceptibility for PDP. Proteogenomic approaches may be helpful to identify role of genes and protein variants in the disease pathology and drug and dosage related adverse effects.
Objective: This study aimed to explore the current understandings of PDP proteogenomic biomarkers in form of single/multiple gene or proteins.
Methods: This meta-analysis study was performed from PubMed database using search terms- "psychosis", "dopamine", "Parkinson or PD", "(psychosis) AND (Parkinson)" including all the clinical trials, prospective/ retrospective cohort studies, case-control studies and cross-sectional studies which reported the PDP. The data related to genetic polymorphism was extracted and analysed. Data related to gene/protein expression in psychosis and PD based on mass spectrometry and ELISA based experiments was checked and analysed.
Results: On search we obtained 2,609 articles, 92 from citing references. On filtering and removal, 39 original research articles related to genetic polymorphism and 7 articles related to mass spectrometry and ELISA were meeting our inclusion criteria (gene/ protein polymorphism and expression-based studies). A few proteomics studies were based on checking the drug effects of pimavanserin, an antipsychotic drug used for the treatment of hallucinations and delusions associated with PDP. We excluded these studies from our analysis. The detailed analysis will be presented with implications for developing precision medicine tailored to PD patients.
Conclusion: The present study is crucial update in current understandings of PDP. Since many genes and proteins are related to dopamine pathways and polymorphism of these could be responsible for genetic susceptibility causing psychosis in PD patients.

ELUCIDATING MICROGLIA PROGRAMS UNDER PARK7/DJ-1-DEFICIENCY, A GENETIC CAUSE OF PARKINSON'S DISEASE

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Microglial cells are the immune effectors of the brain playing critical roles in neurodevelopment, neuroprotection and immune surveillance in the central nervous system. Neuroinflammation and oxidative stress are hallmarks of Parkinson's disease (PD), and linked to a continuous activation of microglia and their loss of neuroprotective functions. Up to 10% of PD cases has a genetic cause, such as mutations in *PARK7* leading to DJ-1 deficiency, which results in early-onset autosomal recessive PD. DJ-1 has a plethora of functions, whereas protection against reactive oxygen species is the best characterized. However, the reason why DJ-1 deficiency leads to early-onset PD is still enigmatic. PD symptoms are caused by the loss of dopaminergic neurons in the midbrain and substantial evidence shows microglia activation in various brain regions in the early phases of the disease. This project therefore aims at investigating the role of microglia during DJ-1 deficiency. Our experiments conducted in a DJ-1 knockout mouse model show that the loss of DJ-1 induces an immune alerted microglia phenotype displaying a downregulation of homeostatic genes and upregulation of disease-associated microglia markers at baseline. Our results further point toward an upregulation of genes involved in phagocytosis and cytoskeleton organization. In addition, DJ-1 deficient microglia demonstrate a higher ability to phagocytose beads compared to wild-type microglia *ex vivo* following LPS stimulation. These preliminary results point toward an immune-alerted microglial phenotype, which we are currently further characterizing. We believe that studying microglia in genetic PD is critical for the understanding of molecular mechanisms underlying neurotoxic processes and for identifying targets protecting against neuronal death. The molecular changes underlying functional alterations in microglia are especially relevant as targeting these programs could be neuroprotective and a future therapeutic in PD.

THE RELATIONSHIP BETWEEN PARAOXONASE 1 (PON1) GENE POLYMORPHISM AND PARKINSON'S DISEASE RISK IN THE NORTH INDIAN POPULATION

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Background: PON1 (paraoxonase 1) gene located on chromosome 7q21.3, is a serum arylsulfatase found to be involved in PD aetiology by having protective effects on PD and low-density lipoprotein from oxidation. It is mainly expressed in liver and hydrolyses organophosphate ester containing pesticides. Two of the mainly reported PON1 gene polymorphisms- Leu55Met and Glu192Arg impairs enzyme activity leading to decrease in m-RNA and protein expression levels in PD patients. Controversial data has been presented among different country populations related to risk for PD based on these genetic polymorphisms, whereas Leu55Met being tested highly. This study was performed to analyse whether PON1 L55M gene polymorphism are associated with an increased PD risk in our North Indian population.
Methods: Blood serum samples were collected from PD patients (n=74) and healthy controls (n=74), age and gender matched. PON1 gene polymorphism at codon 55 (L & M allele) has been studied with polymerase chain reaction amplification and restriction endonuclease digestion.
Result PON1 L55M genotypes was not significantly associated with and PD in this study. However, regression analysis for MM genotype was found 3.18-fold (95% CI 0.32–31.59), which was larger than other genotypes, but with non-significant P-value. The reason for this due to PD patients were dependent on consuming mostly well-water (12.2%), exposed to pesticides-organophosphates (28.4%) and type-2 diabetes (10.8%), significantly higher compared to controls (P-value <0.05). After adjusting the confounders odds ratio (OR) analysis with non-significant P-value showed a slightly decreased OR of LM genotype, MM genotype and M allele. This study used a smaller population from specific locations of India and there is selection bias in terms of not including the environment as major risk factor and regional/ethical/genetic heterogenous population in country like India.
Conclusion: To the best of our knowledge, this is the first study that has investigated the association of PON1 L55M gene polymorphism with PD in the North Indian population. However a positive correlation has been reported in many other ethnic populations across globe. The present study highlights that natural history of PD differs from patients to patients and in different ethnic groups. However larger population-based studies would be required which can be first step delineating role of proteomics in management of Parkinson's Disease.

GENOME WIDE ASSOCIATION FOR AFRABIA PARKINSON'S PATIENTS: HOW FAR HAVE WE COME?

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Background: Parkinson's disease (PD), the most prevalent motoric neurodegenerative disease, has been intensively studied to better comprehend its complicated pathogenesis. Over 80% of genome-wide association studies have been performed on people of European descent, demonstrating a paucity of variety in the field of human genetics. Disparate representation may lead to inequities that inhibit the fair adoption of customized therapy and can also reduce our understanding of disease causes. The AfrAbia population is understudied regarding Parkinson's disease (PD), despite PD being a worldwide condition. No studies of either prevalence or incidence have been conducted yet. Few investigations on the genetic risk factors for PD in AfrAbia communities have been reported. **Objective:** Herein, we performed a dynamic and longitudinal bibliometric analysis to explore the previous studies on PD genetics in AfrAbia region and draw attention to data gaps and promising new research directions.
Methods: All PD publications focusing on PD genetics were retrieved from the PubMed/MEDLINE database using the search strings "Parkinson's Disease" "Genetics" and "Africa". Using filters, only English articles published between 1992 and 2023 were selected. English-language, original research papers revealing genetic findings on PD in non-European African group were considered for inclusion. There were two rounds of independent reviewers that found and retrieved relevant data. The Bibliometrix and Biblioshiny packages from R software were used to conduct the bibliometric analysis.
Results: There is no available paper that focus on PD genetics on AfrAbia patients. The filtered search identified 42 articles (published between 2004 and 2022), including: 2 case reports, 1 historical article, 1 comparative study and 38 journal articles. The first paper was published in 2004. There was an increased trend in the number of articles published. The annual scientific production was highest in 2021 with 5 articles compared with 1 in 2004, with an annual growth rate of 3.93% and 7.17% co-author per document. In terms of cumulative source dynamics, Parkinsonism and related disorders journal was the most mentioned journal with 6 articles compared with 2 in PLOS and only 1 in several journals. Country wise, Sudan was the most contributing country (16), followed by Senegal (7), then Morocco (6). Regarding word dynamics and cloud, humans was mentioned in 32 arti, PD 24 art., mutations in 14 and genetics only in 8 articles. In terms of research and scientific collaboration in this field, most of collaboration were South-North teams with the United States is in the lead, followed by Netherland and Europe. South-South collaborations were mainly between Nigeria and South Africa (3 art), Mali (1 art), and Tanzania (1 art). Also, there was a collaboration between Sudan and Saudi Arabia (1 art); and between South Africa and Mali (1 art), and Tanzania (1 art). According to the thematic evolution analysis, between 2004-2016, black people, humans and prevalence were used simultaneously, however, since 2017, PD has frequently been discussed within the same cluster.
Conclusion: This analysis sheds light on the pressing need for more diverse participant populations in PD studies. Early indicators offered here may be used to monitor future development in PD genetics in the AfrAbia population; this is in line with the goals of the Global Parkinson's Genetics Program (GP2) and similar programs, which are intended to affect research in URPs, including AfrAbia. AfrAbia Consortium may be the realistic solution for this dilemma.

IDENTIFICATION AND FUNCTIONAL CHARACTERIZATION OF VPS41 AS A POTENTIAL GENETIC MODIFIER OF PENETRANCE IN P.G2019S LRRK2-ASSOCIATED PARKINSON'S DISEASE

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Abstract: Trait- or disease-associated genetic variants contribute to substantial variability and penetrance of complex traits and diseases in humans. While several causative genes and risk factors have been identified in familial forms of Parkinson's disease (PD), it remains unclear how patient's genomes shape the predisposition to develop PD. Mutations in LRRK2 are the most common autosomal dominantly inherited form of PD. The p.G2019S mutation displays incomplete penetrance and even within the group of affected individuals a broad range of age at disease onset (AAO) is observed. Through a whole genome sequencing approach in multiple families with p.G2019S LRRK2-associated PD, we have detected rare and common variants that might act as genetic modifiers of AAO. However, prioritizing disease-modifying variants and understanding their biological action remain a challenge.

Using a new scoring system, we prioritized coding variants acting as modifiers of AAO in these families for functional in vitro validation. Among these modifiers we find GO term enrichment for genes with association to "neuron projection" but also Golgi apparatus associated vesicle and transport. From the candidates we selected the missense variant p.E432K in VPS41 (a member of the HOPS complex essential in lysosome/endosome trafficking), predicted by segregation analysis to confer protective effect on AAO in one of the families analysed.

To this end, we assessed LRRK2 phenotypes in patient iPSC-derived dopaminergic neuron cultures. We found that VPS41 knockdown (KD) results in neurite outgrowth indistinguishable between p.G2019S and isogenic WT LRRK2 neurons. Lysosome and endosome morphology was altered upon VPS41 KD, but independent of LRRK2 status. The overexpression (OE) of WT and p.E432K VPS41 in HEK293T cells showed a differential starvation response, with increased localization of TFE3 to nuclei under baseline and starved conditions. In contrast, decreased TFE3 protein levels were previously reported in PD post-mortem substantia nigra compared to healthy controls. Through protein interaction assays we found that p.E432K VPS41 displays increased affinity to RAB7A indicating an increased interaction at the endosome/lysosome interface that is reported to be impaired in p.G2019S LRRK2 mutant neurons.

Our findings lend support the concept of disease modifying variants incrementally contributing to the differential risk to develop PD in the context of LRRK2 mutations. We are currently further investigating how p.E432K VPS41 affects neurite outgrowth, endosome/lysosome morphology and autophagy in patient derived neurons and their controls.

DATA-DRIVEN SUBTYPES OF PARKINSON'S DISEASE USING MACHINE LEARNING IN LUXEMBOURG PARKINSON STUDY

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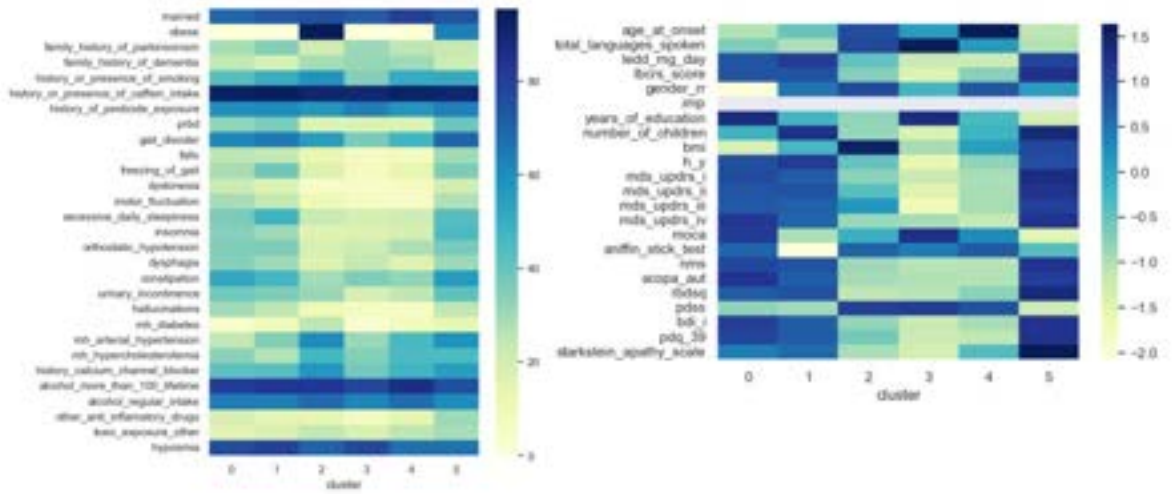
Parkinson's disease (PD) is characterized by variegated clinical manifestations with different grades of motor and non-motor symptoms, and different biomarkers. With the aim to classify the multifariousness of PD in distinct subtypes and study their distinct clinical phenotypes we used machine learning methods like random forest and K-mean clustering in Luxembourg Parkinon's study. six subtypes were identified first using k-mean clustering. We then used linear regression and random forest to identify significantly different clinical characteristics of each of the subtypes. Visualization and statistical analysis were performed for analyzing the obtained PD subtypes. As a result, 704 patients with idiopathic PD from the baseline data were investigated and six subtypes were identified with107,108,111,129,132,117 PD patients respectively. The distinct and statistically significant clinical phenotype differences across these six subtypes are summarized in visual representation through heat plots below.



Further work to elucidate the distinctiveness of the subtypes and looking at difference in molecular signatures across different omics platforms along with refining the subtypes is under future pipeline

ANALYSIS OF INSULIN RESISTANCE AS A RISK FACTOR FOR PARKINSON'S DISEASE

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Recent evidence indicates shared disease mechanisms between Type 2 Diabetes (T2D) and Parkinson's disease (PD), suggesting that T2D may contribute to the development and progression of PD. Insulin resistance, which is the main hallmark of T2D, has also been shown to play an important role in neurodegeneration by altering neuronal metabolism, functionality and survival.
To understand the importance of insulin signalling in the human midbrain we expose human midbrain organoids from healthy individuals and GBA-N409S mutation-carrying PD patients to either high insulin concentrations, leading to insulin resistance, or to low insulin concentrations to restore normal insulin function. We characterise midbrain organoid transcriptional and metabolic profiles in order to identify the most insulin signalling dependent dysregulated cellular processes. Furthermore, we show that insulin resistance compromises dopaminergic neuron maturity and increases cellular death. Our study suggests that defective insulin signalling contributes to the vulnerability of dopaminergic neurons that may lead to the development of PD and aggravates existing PD phenotypes. These results highlight insulin resistance as an important target in PD prevention and therapy

VALIDATION AND ASSESSMENT OF PREDICTIVE ABILITY FOR A POLYGENIC SCORE ON PARKINSON'S DISEASE

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Idiopathic Parkinson's disease (*PD*) is a complex multifactorial disorder with a heritability of ~ 27% for which about 90 SNPs with genome-wide significance have been recently identified.
However, by including non-genome-wide-significant SNPs, the genetic influence can be explained more comprehensively. This can be achieved by using polygenic scores (*PGSs*), which combine the effects of a large number of genetic variants on the risk for a disease such as PD in a single value.
Evaluating the performance of an existing PGS in independent datasets is a mandatory step before it can be established as a valid tool for research.
We therefore examined a previously published PGS for PD [Nalls 2019] for its ability to distinguish between cases and controls in an independent genetic dataset, comprising 1914 PD cases and 4464 controls and were able to replicate the findings.
Furthermore, we theoretically assessed its ability to predict the development of PD for healthy individuals in later life. Here, our main objective were age-stratified predictive values, as these determine the use of this PD-PGS as a prognostic tool.
We concluded that although the PGS for PD introduced by Nalls et al. is a promising tool for research, its ability to predict PD on an individual level based on this PGS alone is not feasible [Koch 2021].

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MODELLING DIGENIC PARKINSON'S DISEASE IN A STEM CELL MODEL CARRYING MUTANT N370S IN THE GBA1 GENE AND THE HOMOZYGOUS DELETION OF EXON 3 OF PARK2

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Background: Parkinson's disease (PD) is the most common neurodegenerative movement disorder worldwide (Bloem et al., 2021). Variants in the ***GBA1*** **gene encoding** the lysosomal enzyme β-glucocerebrosidase (Gcase) **are common genetic risk factors for developing** PD. GBA-PD is characterized by a late disease onset, the presence of cortical Lewy bodies and increased α-synuclein accumulation linked to misfolded Gcase and reduced Gcase enzymatic activity (Do et al., 2019). Moreover, homozygous deletions in the Parkin gene (*PARK2*) have been associated with autosomal recessive forms of PD (Ron et al., 2010). Parkin-PD is marked by an early age of onset and Lewy Body formation only in rare cases (Hayashi et al., 2000). Parkin plays a pivotal role in the ubiquitination of various proteins (Wang et al., 2020), including mutant Gcase variants. Genetic diagnosis of a Parkinson's patient from Italy revealed that he was carrier of a heterozygous GBA N370S mutation and a homozygous deletion of *PARK2* exon 3. Co-occurrence of two disease-associated mutations (triallelic genotype) can lead to three different outcomes: (i) an additive effect, (ii) a synergistic effect both leading to a more severe phenotype than the single mutations, or (iii) an epistatic effect resulting in a different phenotype than expected from adding the effects of the two mutations.
Objective: We aim to study the combined effect of the GBA N370S mutation and loss of Parkin on patient-derived midbrain dopaminergic neurons by cellular phenotyping and comparison with neurons derived from single mutation carriers and isogenic controls.
Results: Midbrain dopaminergic neurons differentiated from the triallelic stem cell model derived from the PD patient, revealed an epistatic interaction between Parkin and GBA. Indeed, lower intracellular α-synuclein protein levels, as well as higher release of α-synuclein into the extracellular space and reduced *SNCA* gene expression were observed in 35-day old GBA-Parkin double mutant neurons compared to control neurons and isogenic neurons with loss of Parkin only. Furthermore, our results showed that Gcase enzymatic activity is lower in mutant GBA-Parkin neurons compared to control neurons. However, mutant GCase is protected from proteasomal degradation in neurons when co-occuring with loss of Parkin compared to GBA N370S carrying neurons with normal Parkin levels.
Conclusion: In this study, we describe an epistatic relationship between GBA and Parkin mutations respective to α-synuclein protein- and gene expression based on measurements in iPSC-derived neurons. Moreover, we provide evidence that mutant GCase, which is known to have reduced enzymatic activity but is redirected towards proteasomal degradation, is protected from proteasomal degradation in the absence of Parkin. Therefore, we hypothesize that Parkin-mediated ubiquitination of mutant GCase is essential for proteasomal degradation of mutant GCase. In the absence of Parkin, the rest activity of the mutant GCase that is not degraded leads to an amelioration of cellular phenotypes.

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COMPARING MULTI-OMICS DATA ANALYSIS APPROACHES ON THE METABOLIC AND miRNA EXPRESSION DATA FROM NCER-PD STUDY

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Parkinson's disease (PD) is one of the most common neurodegenerative diseases globally. Comprehensive understanding of PD requires interpretation of the molecular intricacy and variations at multiple levels such as genome, epigenome, transcriptome, and metabolome. Multi-omics data analysis enables us to get the insight of the biological information flow through various levels to understand the disease mechanism of PD. In this work, we collected metabolic and miRNA expression data from 776 samples from the NCER-PD study, then we implemented and assessed three multi-omics analysis approaches on this data: Similarity Network Fusion (SNF)1, DIABOL2 and Multi-Omics Factor Analysis (MOFA)3,4. The analysis was run on each single omics dataset and on the multi-omics level where performance of these three methods were assessed and similarity clusters between the metabolic and miRNA data were calculated. The correlation between the miRNA and metabolic data (Figure 1) and the cluster of combining datasets (Figure 2) were presented here. Several similar clusters were observed from all these three methods. This approach could be easily extended to other omics data in the PD domain.

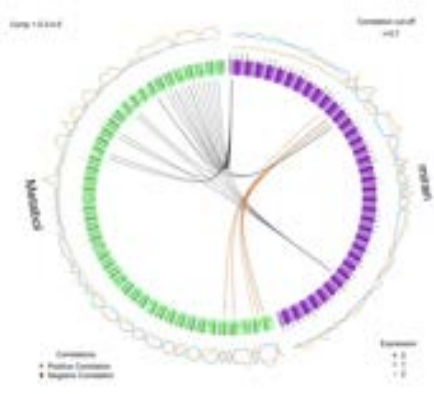

Figure1. Circleplort of the Correlation between dataset with DIABOL miRNA and Metabolic data.

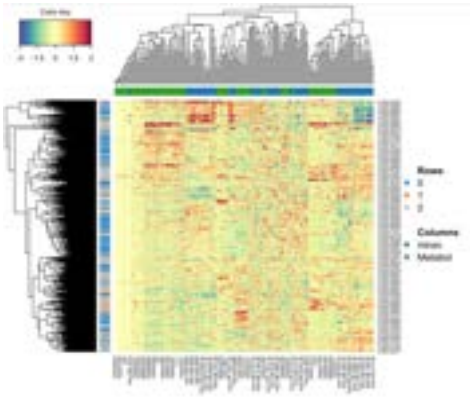

Figure2. Heatmap of combined

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PARKINSON'S DISEASE-ASSOCIATED MUTATION IN MIRO1 LEADS TO MITOCHONDRIAL IMPAIRMENTS AND DOPAMINERGIC NEURON DEGENERATION

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Selective loss of dopaminergic neurons in the nigrostriatal pathway is the main characteristic of Parkinson's disease (PD). Neurodegeneration in PD is believed to occur in a retrograde fashion, with mitochondrial dysfunction being one of the shared features of both monogenic and idiopathic cases. Miro1 (gene: RhoT1), an element of the motor/adaptor complex, is a key regulator of mitochondria morphology, movement and Ca2+ buffering capacity. Interestingly, recent publications reported Miro1 mutations as possible cause of PD, and showed that Miro1 function is altered in fibroblasts of PD patients (monogenic and idiopathic). These suggest a broad involvement of Miro1 in the PD pathology, supporting the hypothesis that Miro1 might represent a convergent path in the onset and/or progression of PD, namely through mitochondrial defects. We hypothesize that mitochondrial damage present in PD patients is dependent on Miro1 function and alterations in the Miro1 pathway might be tolerated until a certain tipping point after which neurodegeneration occurs. To assess our hypothesis, midbrain organoids (MO) derived from induced pluripotent stem cells of a PD patient caring the Miro1 p.R272Q mutation were used. Our MO model resembles the human midbrain, area affected in PD, and is able to reproduce PD pathological phenotypes.
MO were characterized at days 20, 30 and 60 of culture. First, Miro1 R272Q MO showed a lower amount of tyrosine hydroxylase (dopaminergic neuron marker) and higher fragmentation index, from day 30 onwards, comparing with healthy MO or isogenic control MO. Then, despite the similar amount of mitochondrial mass observed (TOM20 and VDAC), Miro1 R272Q MO presented a lower basal respiration and ATP production, lower mitochondrial membrane potential and higher mitochondrial ROS at day 35 of culture – peak of neuronal differentiation. Moreover, principal component analysis of the MO intracellular non-polar metabolites showed a clear separation between the 3 groups (healthy MO, Miro1 R272Q MO and isogenic control MO), with Miro1 R272Q MO presenting an overall reduction in both glycolysis and the TCA metabolites.
At the same timepoint, mitophagy and autophagy pathways show a tendency to be reduced in Miro1 mutant organoids, which might explain energetic deficits observed. However, a deeper analysis in terms of the mitophagy process is needed. Altogether, our results support the hypothesis of Miro1-dependent mitochondrial damage in dopaminergic neuron degeneration and support the role of Miro1 as a possible common molecular target in PD

IDENTIFICATION OF PARKINSON'S DISEASE-ASSOCIATED REGULATORY VARIANTS IN NEURONAL AND NON-NEURONAL CELL TYPES

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Abstract. Parkinson's disease (PD) is the second most common neurodegenerative disease characterized by the loss of dopaminergic neurons located in the substantia nigra of the midbrain and resulting into the wellcharacterized movement disorder. Although rare genetic mutations are responsible for familial PD, for sporadic PD a more complex contribution of common single nucleotide polymorphisms (SNPs) was identified through genome-wide association studies (GWAS) and the underlying genetic causes of PD remain unknown. Many disease-associated SNPs have been found to be enriched within gene regulatory elements that harbor unique sets of transcription factors (TFs) to control cell identity and disease state. Disruption of TF binding due to the presence of a variant within a transcription factor binding site (TFBS) can result in gene expression changes of their putative target genes through cis-regulatory variation. To better understand how PD-associated SNPs may affect dopaminergic neurons and their regulatory landscapes, we generated time series transcriptomic and open chromatin data (ATAC-seq) of human neural precursor cells differentiated into dopaminergic neurons and astrocytes that we overlapped with a PD GWAS-hit catalogue (Nalls et al., 2019) containing about 17 million PD SNPs. Filtering PD SNPs based on genome-wide significance ($p<10^{-8}$) and using a novel approach identifying and associating regulatory elements and their target genes, we detected 3 PD SNPs that create TFBS for LIM homeobox 1 (LHX1), zinc finger and BTB domain containing 14 (ZBTB14) and nuclear receptor subfamily 2 group C member 2 (NR2C2) in human dopaminergic neurons and astrocytes. In our project, we are currently validating the most promising novel regulatory variants in Parkinson's disease-relevant cell types, which not only allows to better characterize the molecular pathways involved in neurodegeneration, but also may provide new avenues for future therapeutic interventions.
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DEVELOPMENT OF SMALL MOLECULE COMPOUNDS TARGETING ALTERED AUTOPHAGY IN PARKINSON'S DISEASE SPECIFIC MICROGLIA.

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Parkinson's disease (PD) is, after Alzheimer's disease, the second most prevalent neurodegenerative disorder. The main pathological characteristic of PD is the degeneration of dopaminergic neurons in the substantia nigra of the midbrain, which triggers the aggregation of a key protein, α-synuclein, and the appearance of the so-called Lewy pathology. Microglia, the innate immune cells of the brain, have been previously described to be critical for PD pathogenesis. They play a key role as the first line of defense of the CNS in case of infections, but they also play physiological role in synaptic homeostasis, maintenance, and functioning. In addition, they can have deleterious (pro-inflammatory phenotype) and/or positive effects (pro-repair phenotype) in different types of brain disorders. We hypothesize that deregulated autophagy in PD patient-specific microglia contributes to their deleterious activity during disease progression.

In this project, we will derive human microglia and midbrain organoids from induced pluripotent stem cells (iPSCs) following a previously published protocol (Haenseler *et al.,* 2017; Monzel *et al.,* 2017). This will include healthy controls as well as a Parkinson's-specific line with a defined mutation, the SNCA triplication, and the matched isogenic control in which the mutation is corrected. Subsequently, patient-specific microglia will be integrated into human midbrain organoids, which were generated from the same iPSC cell lines (Sabate-Soler *et al.,* 2022). With this integration, we will investigate the effect of microglia on dopaminergic neuron degeneration and disease-associated protein aggregation. Furthermore, iPSC-derived microglia will be CRISPR/Cas9 engineered with a fluorescent autophagy reporter, which is suitable for high content imaging and screening (Arias-Fuenzalida *et al.,* 2019). Eventually, we will use this system to screen the available natural compound library for small molecule compounds targeting altered autophagy in PD-specific microglia.

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CHARACTERIZING THE ROLE OF BRAIN RENIN ANGIOTENSIN SYSTEM IN THE PATHOPHYSIOLOGY OF NEURODEGENERTIVE DISEASES

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Background: Dementia currently affects more than 50 million globally with an expected tripling over the next 20 to 30 years (WHO,2022). Post-mortem brain tissue studies showed increased Angiotensin converting enzyme 1(ACE-1) (2) activity and decreased ACE2 level (3) with neurodegeneration. However, the vascular theory of the brain renin-angiotensin system (RAS) in human neurodegeneration has got less focus among brain studies (fig.1).
Aims: This owes to several transitions from a debate over its site- characterization inside the brain up to the nature of changes in its regulators between the diseased and healthy individuals. A controversy has raised regarding the pathological similarity among the different neurodegenerative-disease models and the human brain tissues, as simulators to the real process. Consequently, I have tried to address these hindering gaps for the progression of the dementia research.
Methodology: Primarily, I have included post-mortem human brain tissue with an acceptable post-mortem delay for both healthy and dementated individuals with either Alzheimer`s or Parkinson`s disease. Additionally, I have adopted a non-conventional bio-imaging technique, immunofluorescence unlike the commonly used protein assays, for characterisation of ACE-1 and ACE2 as main key regulators of the brain RAS (fig.2). Moreover, I have been working on measuring the difference in expression of these key regulators between dementated and non-dementated individuals regarding the variation in fluorescence, using a colocalization protocol with neurons, endothelial cells, and astrocytes. ELISA technique will be used for complementary estimation of both the level and the activity of these key regulators in human brains.
Results: Neuronal, astrocytic and vascular distribution of both ACE-1 and ACE-2 in both the frontal and temporal regions of the brain in both dementia and health at variable levels.

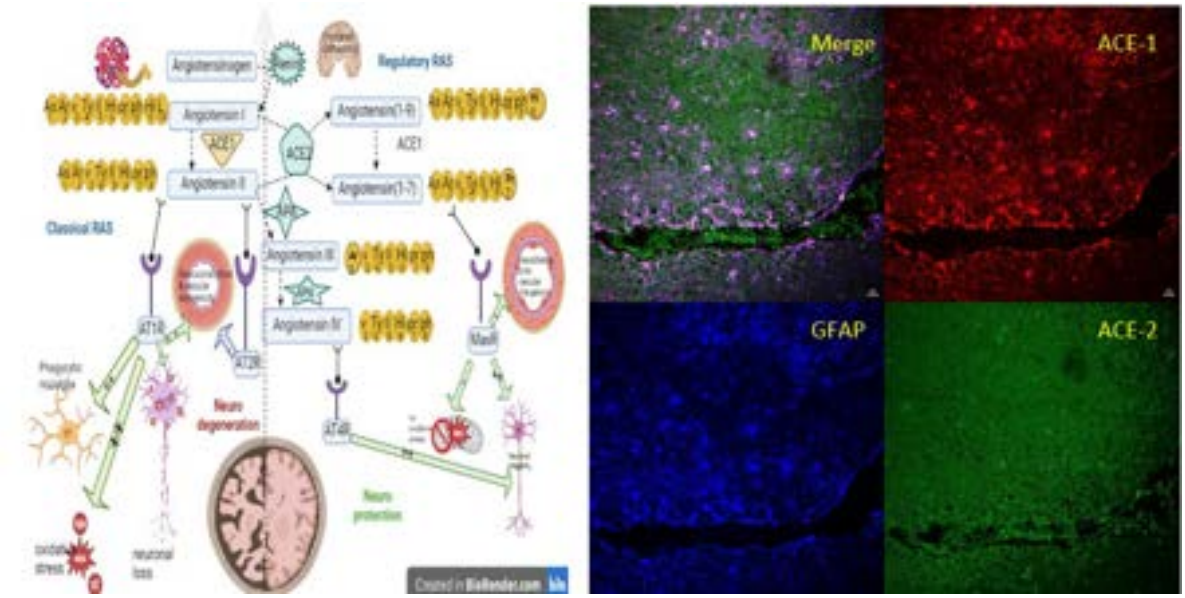

Figure 1: Systemic and brain RAS in health and disease	Figure2: Triple IF staining oF ACE1,2&GFAP

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FUNCTIONAL VALIDATION OF A MITOCHONDRIA-SPECIFIC POLYGENIC RISK SCORE IN PATIENT-BASED MODELS FOR STRATIFICATION OF IDIOPATHIC PARKINSON'S DISEASE

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Objective: The overall objective of this project is to gain essential knowledge on the contribution of genetic variability in nuclear-encoded mitochondrial proteins to idiopathic Parkinson's disease (iPD) pathogenesis. Starting from genomic data, we aim to functionally validate mitochondrial polygenic risk profiles in patient-based cellular models, thus defining mitochondrial pathways potentially involved in neurodegeneration in subgroups of iPD patients.
Background: A large body of evidence specifically points to mitochondrial dysfunction as major cause of PD pathogenesis. Given that only ~10% of PD cases can be attributed to monogenic causes, we hypothesize that a fraction of iPD cases may harbour a pathogenic combination of common variants in mitochondrial genes ultimately resulting in mitochondrial dysfunction.
Method: To decipher this mitochondria-related "missing heritability", we used GWAS common SNPs (MAF ≥ *1*%) data from the Luxembourg Parkinson's study (412 iPD patients and 576 healthy controls), and calculated mitochondria-specific polygenic risk scores (mitoPRS) to capture the cumulative effect of common variants in mitochondrial genes on PD risk. The COURAGE-PD consortium (7270 iPD and 6819 healthy controls) was used as a replication dataset. Skin fibroblasts and iPSC-derived neuronal progenitor cells from iPD patients were identified based on their mitoPRS and then subjected to a comprehensive mitochondrial phenotyping.
Results: We found that distribution of mitoPRS was significantly associated with PD in both Luxembourg Parkinson's study and COURAGE-PD. Extending the PRS approach to selected mitochondrial pathways, we demonstrated that common variants in genes regulating *Oxidative Phosphorylation (OXPHOS*-PRS*)* were associated with a higher PD risk (OR=1.31[1.14-1.50], FDR-adj *p*=5.4e-04 and OR=1.23[1.18-1.27], FDR-adj p=1.5e-29, respectively for the Luxembourg Parkinson's Study and COURAGE-PD). Functional characterization of skin fibroblasts and corresponding iPSC-derived neuronal progenitor cells from iPD patients classified based on *OXPHOS*-PRSs revealed significant alteration of mitochondrial oxygen consumption rates in the high *OXPHOS*-PRS group. Finally, individuals with high *OXPHOS*-PRS tended to have earlier AAO and longer disease duration compared to low-risk patients, a phenotype particularly significant in the larger COURAGE-PD dataset.

Conclusion: We developed and functionally validated novel mitochondria-specific PRSs that could be used as a genetic tool to stratify the heterogeneous group of iPD patients. Using patient-based models relying on these mitochondrial signatures for drug screening approaches may pave the way for future more tailored therapeutic strategies.

ENGINEERING MIDBRAIN-SPECIFIC ASSEMBLOIDS WITH MICROGLIA FOR ADVANCED DISEASE MODELLING

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Organoids are 3-dimensional cell cultures systems that mimic human organs, recapitulating their cellular complexity, structure and function. We developed a protocol to generate Parkinson's disease patient specific midbrain organoids. These midbrain organoids contain all the cell types of the neuro-ectodermal lineage, such as neurons, astroglia, precursor cells and stem cells.

To complete the model with the mesoderm-derived immune-compartment, which is absent in the system, we derived microglia precursor cells from human induced pluripotent stem cells and integrated them into the midbrain organoids. For the first time, and thanks to a specific culture medium that allows dopaminergic neuron differentiation and microglia survival, we developed a midbrain-immune assembloid model with functional microglia.

This advanced midbrain-immune assembloid model will be applied for the study of neuro-immune interactions in physiologic conditions as well as for in vitro modelling of Parkinson's disease.

ALTERATIONS IN NEURON-DERIVED EXOSOMAL CARGO IN PARKINSON DISEASE

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Background: Parkinson disease (PD) is the second most frequent neurodegenerative disease, is characterized by impaired dopamine signaling due to the loss of dopaminergic neurons and this neuronal loss is directly linked with accumulation of α-synuclein.
Exosomes are small extracellular vesicles, which are secreted from many cell types and regulate a plethora of biological mechanisms in the recipient cells. Several studies have linked the exosomal function/cargo with PD, as exosomes contain PD-related proteins, mRNAs of PD-related genes and miRNAs, that regulate PD-related spreading.
Objectives: The main objectives are 1) the confirmation of exosome isolation, based on iPSC-derived midbrain neuron model, 2) the identification of α-synuclein cargo of PD-patient derived exosomes in comparison with the isogenic control-derived exosomes, 3) identification of differences in exosomal proteins, mRNAs and DNA content between PD patient-derived and control midbrain neurons.
Methods: iPSC-derived midbrain neurons of a human carrier of the SNCA Triplication (AST23) and its isogenic control were used as cell model. We set up an efficient exosomal isolation method. Obtained exosomes were characterized with Western blot analysis (WB), nanoparticle tracking analysis (NTA) and transmission electron microscopy (TEM). Finally, we isolated total exosomal RNA and DNA, in order to quantify our genes of interest with qPCR and total exosomal extract for WB.
Results: We differentiated AST23 smNPCs and the isogenic control into midbrain neurons (enriched for dopaminergic neurons), from which we successfully isolated a highly enriched exosomal fraction. Concerning exosomal protein cargo, we confirmed the presence of α-synuclein inside exosomes of both cell lines and we identified differences in the protein levels of lysosomal protease cathepsin D and in the protein levels of PARK7 (DJ-1). We identified increased mRNA levels of both PARK7 (DJ-1) and PINK1 in the SNCA triplication-derived neuronal exosomes in comparison with the respective isogenic control-derived neuronal exosomes, that were accompanied by increase in the mitochondrial DNA levels.
Conclusion: Our results revealed alterations in the exosomal-sorted lysosomal proteins, PD-related gene transcripts and mtDNA. Yet it is not clear, whether these changes are ''surrogate biomarkers or may directly related to pathogenic pathway. Further research is needed, as exosomes can reveal new mechanisms of PD spreading, putative PD biomarkers and novel therapeutic targets.

ANALYZING THE METABOLIC FUNCTION OF DJ-1 IN ASTROCYTES TO DEFINE ITS ROLE IN THE PATHOGENESIS OF PARKINSON´S DISEASE (PD) AND GLIOBLASTOMA MULTIFORME (GBM)

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Aims
Here, we are comprehensively studying the function of DJ-1 in PD and GBM to better understand its observed role in neurodegeneration and cancer. Mutations in the PD-associated gene PARK7 leading to loss of function of DJ-1 protein cause autosomal-recessive PD, whereas high levels of DJ-1 protein were found in different cancer like GBM.

Methods
To analyze the role of DJ-1 in the regulation of the metabolic switch of increased glycolysis in cancer and impaired metabolism in PD, stable isotope labeled glucose metabolite tracing was used. Metabolomics analysis was performed using human iPSC derived midbrain dopaminergic neurons, human iPSC derived astrocytes of two different isogenic pairs and DJ-1 overexpression and GBM cell lines (U87, U251 and LN229).

Results
In human iPSC derived midbrain dopaminergic neurons, glucose tracing showed a significantly increased glycolytic and TCA flux in the DJ-1 overexpression line and a decreased TCA flux in DJ-1 deficient neurons. Concordant with the increased TCA flux, we found significantly increased protein levels of pyruvate dehydrogenase in DJ-1 overexpressing neurons. In contrast, glucose tracing in astrocytes revealed that overexpression of wildtype DJ-1 increases the glycolytic and TCA flux. The loss of DJ-1 significantly reduced the glycolytic and TCA flux in astrocytes. The knockdown of DJ-1 reduces the glycolytic and TCA flux in GBM cells.

Conclusions
Our results show that the effect of DJ-1 on the metabolism in neurons, astrocytes and GBM cells is depending on its different protein levels. High levels of DJ-1 in GBM cells support, and low levels of DJ-1 in PD impair the metabolism. Based on the alterations in the glucose metabolism observed, we aim to identify the molecular target of DJ-1 that is responsible for these metabolic phenotypes in PD and GBM models.

PARYLATION OF A-SYNUCLEIN OLIGOMERS IN PARKINSON'S DISEASE PATIENTS: A TRIGGER FOR PROTEIN AGGREGATION

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Abstract. Parkinson's disease (PD) etiology is still not clear and therapies currently pursued are not resolutive. Understanding the mechanism that leads to α-Synuclein aggregation and neuronal death is crucial for designing mechanism-based treatment strategies and, in addition, to identify an early biomarker for timely action. In this field, Poly(ADP-ribosyl)ation (PARylation) has emerged as an important post-translational modification (PTM) catalyzed by PARP1 enzyme, that could be implicated in neurodegenerative diseases [1]. In the context of PD, in *vivo* and in *vitro* studies have proposed PARylation to be able to induce α-Synuclein aggregation, and to activate a mitochondrial-mediated cell death pathway known as Parthanatos pathway [2]. In addition, we previously demonstrated that PARP1 enzyme translocates from neuronal nucleus to cytoplasm in *post-mortem* human brain of PD patients [3]. Based on that, the aim of the present study was to investigate the still unexplored PARylation state in *post-mortem* human brain obtained from patients in the late stage of PD (Braak stage 6), linking it with α-synuclein aggregation. Our results indicate that PAR polymers translocate from nucleus to cytoplasm of neurons, where they co-localize with different form of α-Synuclein aggregates, including Lewy bodies. Moreover, using Proximity ligation assay (PLA) and 3D reconstruction, we focused on α-synuclein oligomers, which are the early stage and considered the main toxic species of aggregation, and demonstrated, for the first time, that they are PARylated. Furthermore, once translocated into the soma of *substantia nigra* dopaminergic neurons, PAR polymers also co-localize with mitochondria in PD patients. All together, these data suggest that PARylation is involved in triggering α-synuclein aggregation and Parthanatos cell death pathway.
Moreover, since an increase of PAR polymers has already been found in the CSF of PD patients compared to controls, we are now moving to investigate PARylation also in the peripheral nervous system using skin biopsies, an already established model in which α-synuclein oligomers accumulates in the autonomic synaptic terminals of PD subjects [4]. This approach could open up the investigation for a reliable biomarker in PD pathology.

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SARS-COV-2 INDUCES DOPAMINERGIC NEURON LOSS IN MIDBRAIN ORGANOIDS

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Abstract. Objectives: COVID-19 presents numerous symptoms mostly associated with the respiratory tract. However, recent evidence showed that the SARS-CoV-2 virus affects the nervous system. We evaluated the effect of the infection in midbrain organoids to determine if cells and pathways related to the onset of Parkinson's disease (PD) are affected.
Methods: The effect of the virus after short- and long-term cultures (4 days, and 1 month) post-infection was analyzed. Features measured included the degree of dopaminergic differentiation (TH), neurite fragmentation, and the level of activated astrocytes (GFAP and S100beta). Bulk RNAseq was performed to determine the effects of the infection on gene expression.
Results: After infection with SARS-CoV-2, the levels of dopaminergic neurons were significantly reduced in both short and long-term culture. Moreover, neurite fragmentation of TH positive neurons in infected organoids significantly increased respective to controls in long-term cultures. Within the same infected organoid TH/SARS-CoV-2 double positive neurons presented an altered morphology and high degree of neurite fragmentation compared to uninfected TH positive neurons. Activation of astrocytes was significantly reduced after infection in the short-term culture. While the levels of S100beta recovered over time, they still remained lower in infected organoids. In both short- and long-term culture, SARS-CoV-2 colocalized more with certain types of cells showing a marked preference for GFAP positive and TH positive cells when normalized to their respective abundance in the organoid. Gene expression analysis revealed a disruption in gene pathways related to vesicle transport, endosomal and autophagy pathways following infection with SARS-CoV-2.
Conclusions: Infection of midbrain organoids with SARS-CoV-2 induced a clear neurodegenerative process of TH positive neurons, while disrupting main pathways known to be involved in Parkinson's disease.

PHENOTYPIC PROFILING OF HUMAN STEM CELL-DERIVED DOPAMINERGIC NEURONS FOR DRUG SCREENING APPLICATIONS

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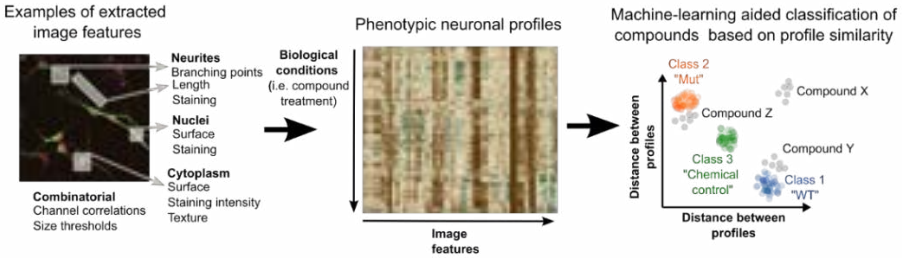
Abstract. Collective evidence connects a diverse set of cell biological processes with midbrain dopaminergic (mDA) neuron loss in Parkinson's disease (PD). Described disease mechanisms converge upon defects in protein degradation, disruption of vesicular trafficking and endolysosomal function, and mitochondrial dysfunction and oxidative stress (Panicker et al., 2021). Current cellular PD models for in vitro drug discovery are often of non-neuronal origin and do not take complex pathological interactions into account and focus on a single readout or phenotype. Possibly because of these limitations, traditional PD in vitro models have not yielded a disease-modifying treatment for PD.

We hypothesized that combining multiple PD relevant cellular phenotypes in disease relevant human mDA neuronal models will increase the accuracy, stability, and usability of such models for drug discovery purposes. Previously we showed in LRRK2 G2019S mDA neurons that image-based multidimensional readouts can detect chemical compounds such as LRRK2 kinase inhibitors or α-synuclein lowering agents (Vuidel et al., 2022). Here we now describe an extension of this phenotypic profiling approach to SNCA gene triplication-carrying stem cell-derived mDA neurons.

Using automated image segmentation, we extracted 126 phenotypic features from microscopic images of SNCA triplication mDA neurons. As expected, we identified known phenotypes such as elevated α-synuclein levels, decreased Tyrosine hydroxylase (TH) levels, and reduced dendritic complexity. We validated our disease model with functional plate-reader assays that showed increased proteasome activity, increased oxidative stress and decreased mitochondrial membrane potential. Next, we screened 1088 mode-of-action annotated small molecules and used machine learning (ML) classification algorithms to identify compound-treatment induced SNCA triplication phenotypic profiles that resembled a presumably "healthy" isogenic control phenotypic profile (Scheme 1). Based on the measured phenotypic profiles, we identified different compound classes that either selectively modified single or larger groups of phenotypes. We are currently evaluating the identified compounds using additional orthogonal assays. We anticipate that profiling approaches that consider an ensemble of phenotypes will eventually lead to cellular models with potentially high predictive value for therapy development.



Scheme 1: From image-extracted phenotypic features to chemical compound classification.

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PINK1-PD NEURONS DISPLAY ALTERED TYROSINE HYDROXYLASE PHOSPHORYLATION

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Loss of mitochondrial quality and death of dopaminergic neurons in the *substantia nigra* are key hallmarks of PINK1-Parkinson's Disease (PD). PINK1 is a Ser/Thr kinase that is highly regulated at the mitochondria and is known to phosphorylate several outer mitochondrial membrane proteins thereby mediating PINK1-Parkin mitophagy after mitochondrial depolarization and/or mitochondrial stress. We performed a phospho-proteomic screen with crude mitochondria enriched from PINK1 wildtype (WT) and knockout (KO) human iPSC-derived dopaminergic neurons and found an enzyme - Tyrosine Hydroxylase (TH) to be less phosphorylated at Ser19 in the absence of PINK1. TH is a crucial enzyme known to be involved in the rate-limiting step of dopamine biosynthesis. To validate our findings, we used immunofluorescence imaging and immunoblotting to visualize localization and quantify phosphorylated TH Ser19 respectively, and confirmed that TH is less phosphorylated in PINK1 KO and PINK1 Q126P neurons compared to their WT isogenic controls. The PINK1 Q126P mutation was found in several PD patients and has been shown to affect the stability of PINK1. We also observed a higher nuclear localization of phosphorylated TH Ser19 in PINK1 KO and Q126P mutation neurons. However, the overall protein level of total TH is not significantly affected. We postulate that PINK1 could be directly or indirectly involved in the phosphorylation of TH at Ser19. This reduction of TH Ser19 phosphorylation is known to affect TH activity and may lead to a decreased production of dopamine and other catecholamines. Here, we identify a novel observation in PINK1-PD neurons that could be relevant for the early events in disease etiology.

MIRO1 RETENTION AT DEPOLARIZED MITOCHONDRIA IN PARKINSON'S DISEASE

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Parkinson disease is caused by the loss of dopaminergic neurons of the Substantia nigra. Such neurons are critically dependent on proper mitochondrial function since they require a constant supply of energy and calcium to maintain the integrity of their long axons and to regulate their pace-making activity for the release and recycling of neurotransmitters. Dysfunctional mitochondria undergo mitophagy in normal conditions to avoid their accumulation. Pink1 and Parkin proteins are two key role players to initiate canonical mitophagy by identifying damaged mitochondria. These proteins lead to phosphorylation and ubiquitination events on mitochondrial substrates which leads to their identification for degradation by the proteosome. One of the Pink1/Parkin pathway substrates is the mitochondrial protein Miro1 which was found to be abnormally retained at the mitochondria upon depolarization in a subset of Parkinson's disease fibroblasts [1]. Compounds have been identified that can reverse this phenotype. The goal of our study is to confirm whether Miro1 retention upon mitochondrial depolarization is a robust cellular hallmark of Parkinson's disease (PD) and whether the compound 3-(3-fluorophenyl)-1-(4-{[6-(1H-imidazol-1-yl)pyrimidin-4-yl]Amino}Phenyl)Urea could be used to promote Miro1 depletion using an independent small cohort of human fibroblasts and replication in commercially available fibroblasts used in the study by (Hsieh et al 2019), as shown in the graphical abstract. This work would verify the importance of this biological pathway in PD, strengthen efforts worldwide to find novel compounds for the treatment of PD and complement our research on the role of Miro1 in human dopaminergic neurons.

ALPHA-SYNUCLEIN OLIGOMERS IN SKIN BIOPSY: A RELIABLE BIOMARKER IN IDIOPATHIC AND GBA-ASSOCIATED PARKINSON'S DISEASE

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Parkinson's disease (PD) has been recently redefined as a multisystem disorder not limited to the CNS [1]. Multiple studies reported evidence for the presence of α-synuclein-related pathology in peripheric tissue, mainly affecting the autonomic nervous system. On this basis, α-synuclein has been recently investigated as a putative peripheral biomarker for PD, being this important for diagnosis in alive patients and improving patient stratification for clinical trials. In this field, we used skin biopsies as a simple and minimally invasive model to investigate peripheral nervous system in living patients, and we tested them for the presence of α-synuclein oligomers, considered as the toxic conformation of the protein. By means of proximity ligation assay (PLA) we demonstrated a significant increase in α-synuclein oligomers in idiopathic PD patients compared to healthy controls, and we propose a quantitative parameter (PLA score) that showed good sensitivity, specificity and positive predictive value (82%, 86% and 89%, respectively) [2]. These results endorse the hypothesis that alpha-synuclein oligomers could be taken into consideration as a reliable diagnostic biomarker for PD. In addition, we investigated skin biopsies obtained from a PD-GBA cohort (n=28) including L444P and N370S mutations (n=12 and n=9, respectively) compared to age- and sex-matched healthy subjects (n=28). Our results indicate that PLA score can distinguish PD-GBA patients from age- and sex-matched control subjects ($P<0.0001$) with good sensitivity and specificity (92% and 85%, respectively). Interestingly, a mild correlation was observed with cognitive symptoms, while no correlation was found with motor symptoms and disease duration, despite having reported a more severe disease progression for the L444P subpopulation. All together, these data reinforce the value of PLA score as a reliable biomarker for genetic forms of PD. Likewise, this approach could be useful to shed light on novel neuropathological aspects of PD.

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INVESTIGATING THE ROLE OF DJ-1/PARK7 IN THE IMMUNOPATHOGENESIS OF PARKINSON'S DISEASE

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Background

It has been established that loss of function of DJ-1 protein leads to an early-onset Parkinson's disease (PD) with slow progression by causing mitochondrial dysfunction and degeneration of the dopaminergic (DA) neurons. Our recent studies show that DJ-1 depletion also affects peripheral adaptive immune system by altering its immunoaging profile (Zeng et al., 2022). Moreover, another study on mice demonstrates a significantly higher CXCR4 expression in DJ-1 deficient T lymphocytes, which increased T cells' migration rate towards CXCL12, a natural ligand for CXCR4 (Jung et al., 2014).

Objectives

In this project, we aim to investigate whether DJ-1 deficiency in T cells contributes to dopaminergic neuronal death in PD.

Methods

To address this open question, we aim to build up an in-vitro co-culture model between patient's induced pluripotent stem cells (iPSC)-derived dopaminergic neurons and healthy donors' T cells. T lymphocytes isolated from healthy donors' peripheral blood mononuclear cells (PBMC) undergo DJ-1 knockdown with lentivirus. In migration assay, different concentrations of CXCL12 will be used to induce migration of control and DJ-1 knockdown T cells. In the co-culture experiments using DJ-1 deficient T cells and patient iPSC-derived neurons, including a unique isogenic control, we will analyze various relevant pathways and markers in the neurons and T lymphocytes.

Results

Our previous studies on an animal model demonstrate age-dependent reduction of immunoaging phenotype in T cells of the aged DJ-1 knockout mice. In the same study, we have also compared PBMC of a DJ-1 loss-of-function mutation patient and his two unaffected brothers of a similar age, which confirmed the same cellular phenotype in the PD patient carrying homozygous DJ-1 mutation as observed in the animal model.

Next, we will examine the migration profile of DJ-1 deficient T cells in response to CXCL12, and an enhanced cytotoxic activity of DJ-1 deficient T lymphocytes against neurons and isogenic pair in co-culture models.

Conclusion and Outlook:

Our findings suggest a potential new role of DJ-1 mediating neuronal degeneration in PD via immune mechanisms. We speculate that DJ-1 deficiency in T lymphocytes increases their cytotoxic activity against DA neurons, therefore, contributing to the neuronal degeneration in PD patients affected by DJ-1 mutation. In order to consolidate our findings we will introduce a

dopaminergic neuronal model, including the gene corrected isogenic control that are already available and characterized.
Moreover, we are improving the efficiency of the DJ-1 knockdown in PBMC-isolated T lymphocytes.

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AN IN VITRO AND IN VIVO STUDY OF THE IMPACT OF THE PARKINSON'S DISEASE-ASSOCIATED R272Q MIRO1 VARIANT

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Objective:
The aim of this project is to identify disease-associated cellular phenotypes in Parkinson's disease (PD) patients carrying RHOT1/Miro1 mutations and discover potential new targets to correct impaired Miro1 function.

Methods:
We first assessed mitochondrial function in iPSC-derived neurons from a PD patient carrying the Miro1 R272Q mutation and the corresponding isogenic gene-corrected line. Age and gender-matched controls were also included. Lastly, Bulk RNA sequencing was performed. Moreover, we generated a knock-in mouse model expressing the mouse orthologue of the Miro1 R272Q mutation, i.e. Miro1 R285Q KI mouse, to evaluate the impact of Miro1 deficiency on nigrostriatal pathway's integrity *in vivo*.

Results:
We found that mitochondrial respiration was significantly impaired in Miro1 R272Q-mutant neurons compared to healthy controls and the isogenic gene-corrected line. This phenotype was accompanied by decreased mitochondrial membrane potential (MMP) and ATP levels, and by higher accumulation of reactive oxygen species (ROS) in the Miro1 R272Q-mutant neurons compared to both control lines. RNA sequencing revealed dysregulated gene expression in pathways related to endocytosis, vesicles, as well as axons and neuronal projections.
In vivo, our findings demonstrated a significant reduction of dopaminergic neuron viability in the *substantia nigra pars compacta* (SNpc) of old mice carrying the Miro1 R285Q mutation.

Conclusions:
We highlighted that the R272Q mutation causes alterations in energy metabolism of iPSC-derived neurons *in vitro*. This is consistent with our former study, in which we observed an increase of Mitochondria-ER contact sites and inhibition of mitochondrial clearance. Altered gene expression related to endocytosis and vesicles opens future research possibilities focusing on the aforementioned vesicles, especially exosomes. We confirmed our hypothesis that damaged mitochondria are not degraded, resulting in mitochondrial bioenergetics impairments. Miro1 being a calcium sensor, among other roles, we will investigate the impact of the R272Q mutation on calcium homeostasis. *In vivo*, aging leads to dopaminergic neurons loss in the SNpc of mice expressing the human orthologue R285Q, strengthening the involvement of the former Miro1 mutation in the pathogenesis of PD.

PARK7/DJ-1 REGULATES IMMUNOAGEING IN T-CELL COMPARTMENTS

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Abstract:

Decline in immune function during aging increases susceptibility to different aging-related diseases. However, the underlying molecular mechanisms, especially the genetic factors contributing to imbalance of naïve/memory T-cell subpopulations, still remain largely elusive. Here, we show that loss of DJ-1 encoded by *PARK7*/DJ-1, causing early-onset familial Parkinson's disease (PD), unexpectedly diminished signs of immunoaging in T-cell compartments of both human and mice [1]. Compared with two gender-matched unaffected siblings of similar ages, the index PD patient with DJ-1 deficiency showed a decline in many critical immunoaging features, including almost doubled non-senescent T cells. The observation was further consolidated by the results in 45-week-old DJ-1 knockout mice. Our data demonstrated that DJ-1 regulates several immunoaging features via hematopoietic-intrinsic and naïve-CD8-intrinsic mechanisms. Mechanistically, DJ-1 depletion reduced oxidative phosphorylation (OXPHOS) and impaired TCR sensitivity in naïve CD8 T cells at a young age, accumulatively leading to a reduced aging process in T-cell compartments in older mice. In the meantime, we also found that DJ-1 depletion impairs homeostatic cellularity of the suppressive immune subset, regulatory T cells (Tregs), only in aged mice and the impairment occurs via regulation of the activity of the gatekeeper enzyme pyruvate dehydrogenase (PDH) of the tricarboxylic acid (TCA) [2]. In short, our recent findings suggest an unrecognized critical role of DJ-1 in regulating immunoaging, discovering a potent target to interfere with immunoaging- and aging-associated diseases, such as PD.

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GAIT PARAMETERS FROM INSTRUMENTED TIME-UP-AND-GO IN PARKINSON PATIENTS DEPEND ON GBA MUTATION

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Background: Mutations in glucocerebrosidase gene (GBA) represent the most common genetic risk factor for Parkinson's disease (PD) with overall conversion to PD in 30%. This subgroup of PD patients (PD^{GBA+}) shows a distinctive genotype-phenotype interaction with more malignant motor phenotype and higher rate of cognitive decline. Cognition in PD^{GBA+} has been previously shown to be a relevant factor for gait impairment [1], but how exactly does the GBA stratification translate into clinically relevant wearable sensors-derived gait parameters has not yet been fully understood. Objective: To investigate the differences in sensor-derived spatiotemporal gait parameters during the Time-Upand-Go (TUG) assessment in PD^{GBA+} vs non-mutation carriers with patients with PD (PD^{GBA-}).

Methods: A total of 166 TUG gait assessments have been collected at the Parkinson Research Clinic from 2017 until 2020 (longitudinal cohort study within NCER-PD): 9 PD^{GBA+} (6 low risk pathogenic, 3 severe pathogenic mutations, age=60.2±6.6, UPDRS III=32.33±15.2) and 157 PD^{GBA-} (age=66.1±10.3 years, UPDRS III=33.8±12.5). For the instrumented TUG, the participants wore a sensor-based gait analysis system (Portabiles GmbH, Erlangen, Germany) which derived, from the signals of two 6 axis inertial measurement units positioned on the lateral side of each shoe, 16 spatiotemporal parameters associated to each stride. For each patient, the mean value and the coefficient of variation (CV, stride variance) of all stride parameters has been computed revealing 32 gait parameter features per TUG. Gait features and clinical scores (MOCA, MDS-UPDRSIII, MDS-UPDRSIII sub-items 3.10 and 3.12) were compared between PD^{GBA+} and all PD^{GBA-} using Wilcoxon rank sum test. In a second subset analysis the 9 PD^{GBA+} were matched to 9 PD^{GBA-} by disease duration and age, and compared for their clinical characteristics and gait patterns.

Results: Two of the 32 sensor-derived gait parameters revealed significant differences in PD^{GBA+} vs PD^{GBA-}: CV of landing impact accelerations ($p<0.01$) and CV of stance time ($p=0.03$). After matching by disease duration and age, the landing impact acceleration remained significant ($p=0.02$). The clinical scores did not show significant difference ($p<0.05$) both for the full and the matched dataset.

Conclusion: In our analysis no differences in clinical characteristics could be detected, however, sensor-based assessment of gait revealed two significant parameters differentiating PD^{GBA+} vs PD^{GBA-}, suggesting that sensor-based gait analysis using the instrumented TUG could complement the clinical evaluation. Interestingly, the five additional gait features presenting the lowest p-value without reaching statistical significance were all associated to stride variances. These results are aligned with previous studies that highlighted the key role of symmetry and variability [1] [2]. Physiologically, the difference in the detected parameters (landing impact and stride variances) might be related to an impairment of stability and/or agonist/antagonist synchronization during deambulation, potentially hinting to an affected cortical control of gait in PD^{GBA+}. Nevertheless, larger datasets are warranted to validate these hypotheses.

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Precision Medicine in Parkinson's disease:
Past lessons and conquering new frontiers
26-27 January 2023

COGNITIVE PROFILE IN PRODROMAL PARKINSON'S DISEASE

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Objective: The present study explores the cognitive profile in prodromal Parkinson's disease. We compared people with REM-Sleep Behavior Disorder (RBD) with an age- and gender-matched control group presenting no RBD and no hyposmia.

Background: RBD, a parasomnia characterized by excessive muscle tone and abnormal behaviors during REM-sleep stages, and olfactory dysfunction are considered as strong risk factors for α-synucleinopathies, such as PD [1]. Previous findings reported that at the time of diagnosis, approximately 20% of the newly diagnosed PD patients present with cognitive impairment [2], especially changes in global cognition and executive functions are observed [3]. These changes may precede clinical PD diagnosis by up to 6 years [3]. Knowledge of cognitive impairment in prodromal PD is still limited [4].

Methods: A total of n=88 participants from the Luxembourgish RBD cohort have been included in the study. All participants were assigned to the prodromal PD group (probable RBD and hyposmia; n=44) or the control group (no probable RBD and no hyposmia; n=44) based on the RBD Screening Questionnaire (RBDSQ) [5] (cut-off ≥7) and an olfactory test (B-SIT[6]/ Sniffin'Stick [7]). Both groups were age- and gender-matched. No significant differences were observed for years of education. We excluded people with known neurological and severe psychiatric diseases. The Montreal Cognitive Assessment (MoCA) [8], the CUPRO evaluation system [9], Trail-Making-Task (TMT) [10], the Digit Span [11], Corsi Block-Tapping Task [12], Kaplan Stroop test [13], Frontal Assessment battery (FAB) [14], Semantic and Phonemic Fluency test, the interlocking Pentagons test [15], CERAD Word list [16] and Benton's Judgment of Line Orientation [17] test were applied to assess cognitive functions. The Informant Questionnaire on COgnitive Decline in the Elderly (IQCode) [18], the Beck Depression Inventory (BDI-I) [19], the Starkstein Apathy Scale (SAS) [20] and the Parkinson's Disease Questionnaire (PDQ-39) [21] were applied to assess global cognition, depressive and apathic symptoms as well as quality of life, respectively.

Results: After Bonferroni correction for multiple testing, no significant differences can be observed in the cognitive assessments between both groups. The prodromal group showed a significantly higher depression and apathy score and significantly lower quality of life.

Conclusion: No significant differences in cognition has been observed in the prodromal group compared to their matched control group. Future research will seek to complete these analyses with an increased sample size and in a polysomnography-proven RBD group in the

Luxembourgish RBD Study. Furthermore, longitudinal analysis will evaluate conversion rates to α-synucleinopathies.

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WHY IS THERE OFTEN A "FIGHT OR FLIGHT" BEHAVIOR IN REM SLEEP BEHAVIOR DISORDER?

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REM sleep behavior disorder (RBD) is an abnormal behavior of the rapid eye-movement (REM) sleep, characterized by loss of muscle atonia and various motor behaviours with concordant dream content. This "acting out of dreams" is frequently violent, but soft movements, reminiscent of daily life activities, may also occur. RBD is seen in synucleinopathies, even as a harbinger syndrome. Animal models based on pontine lesions or on pharmacological induction of RBD replicate aggressive / defeating movements. The dysfunctional locus subcoeruleus is (LSC) responsible for the loss of muscle atonia. Interaction with brainstem nuclei such as the pedunculopontine nucleus and the superior colliculi may contribute to the syndrome as well. These nuclei are evolutionarily old, often staying behind the exponential telencephalization. Their dysfunction in synucleionopathies is evidenced by neuropathology and neuroimaging studies, but it remains unelucitated why the LSC is the starting point of the process. Of note, nuclear dysfunction may induce disinhibition of central pattern generators, responsible for automatized basic behaviours. The threat simulation theory also suggests that, similarly to evolutionarily purposeful *mental* rehearsal of threatening life events during REM sleep, there may be *motor* rehearsal of such events during RBD. This could explain why RBD movements are often violent and jerky. Often, they are also faster, as being driven by a direct pathway from the motor cortex to the spinal cord, circumventing the basal ganglia.

While attractive, these evolutionary considerations *cannot* explain *all* the RBD symptoms. Future research should focus on why there are variable trajectories of RBD syndromes and if there are triggering life events. Beyond RBD, these 'solid mental images' should advance our general understanding of dream functions.

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ARE PATHOGENIC GBA MUTATIONS ASSOCIATED WITH A DECLINE IN PATIENT-REPORTED FUNCTIONAL MOBILITY?

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Background: While people with Parkinson's disease (PD) who carry pathogenic GBA mutations have demonstrated a faster decline in the postural instability and gait difficulty (PIGD) phenotype [1], the association of the mutations with the trajectory of patient-reported functional mobility remains unknown.
Objectives: Describe the trajectory of patient-reported functional mobility for people with typical PD or Parkinson's disease dementia (PDD) and evaluate the interaction effect of pathogenic GBA mutations and time on functional mobility.
Methods: We included 736 people with either typical PD or PD dementia (PDD) from the ongoing Luxembourg Parkinson's Study [2] with a yearly follow-up with a total duration of study participation from one to seven years. 75 of 736 (10.2%) participants carried pathogenic GBA variants (severe or mild mutations, or risk variants). We assessed functional mobility by the recently validated patient-reported FMCS [3] with a score from 0 to 100 (higher score = better functional mobility). A longitudinal two-level mixed models analysis (fixed effects: GBA-mutation interacting with time, random effects: subject, random slope: time) was performed to examine the interaction-effect of the GBA mutations and time on functional mobility with the R-package lme4 (function lmer) [4]. We compared differences in functional mobility, age, and disease duration at baseline between people with and without pathogenic GBA variants by two-sided t-tests.
Results: As expected from a chronic progressive disorder, the whole group showed a significant decline in patient-reported functional mobility by -2.17 points ($p < 0.001$) per visit. While we detected no significant group differences at baseline ($p > 0.05$), people with pathogenic GBA variants experienced a significantly more severe decline by -3.6 points per visit ($p = 0.034$) compared to people without -1.96 ($p < 0.001$). Moreover, a change of -3.6 is experienced by people with PD as a meaningful deterioration of functional mobility. Thus, pathogenic GBA-mutations were statistically and clinically significant moderating the effect of time on functional mobility [5].

Conclusion: Compared to people with PD without pathogenic GBA variants, carriers of GBA variants experience a faster decline in patient-reported functional mobility. Pathogenic GBA mutations may be a relevant risk factor in precision medicine for functional mobility.

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COGNITIVE PROFILE IN PARKINSON'S DISEASE PATIENTS CARRYING GLUCOCEREBROSIDASE MUTATIONS

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Objective: The present study explores the cognitive profile in Parkinson's Disease (PD) patients carrying Glucocerebrosidase (GBA) mutations. We compared cognition in people with typical PD carrying pathogenic GBA variants (risk variants, mild or severe risk mutations) to matched GBA mutation negative PD patients.

Background: Mutations in the glucocerebrosidase (GBA) gene are among the most common genetic risk factors for the development of PD. Previous findings have suggested that participants with GBA related PD show an earlier age of onset, more non-motor symptoms and a specific cognitive profile, with a impairment in working memory, executive functions and visuo-spatial processing compared to the idiopathic PD [1]. Few studies did not find differences in cognition, especially in GBA related PD at early disease stages [3].

Methods: A tota number of 104 participants from the Luxembourg Parkinson's Study were included in this cross-sectional analysis. Participants were assigned to GBA related PD group (n = 52) and non-GBA related PD group (n = 52) based on sequencing of the whole GBA gene with the real-time single-molecule sequencing technique developped by PacPio (Pachchek et al. in preparation). Both groups were age- and gender-matched. No significant differences were observed for years of education and disease duration between the groups. The Montreal Cognitive Assessment (MoCA) [4] and the Trail-Making-Test (TMT) [5] were applied to assess global cognition, executive functions and psychomotor speed. The Beck Depression Inventory (BDI-I) [6], the Starkstein Apathy Scale (SAS) [7] and the Parkinson's Disease Questionnaire (PDQ-39) [8] were applied to assess depressive and apathic symptoms as well as quality of life, respectively.

Results: After Bonferroni correction for multiple testing, no signifcant differences were observed in the cognitive assessments between both groups. Furthermore, both groups did not differ significantly for depression, apathy and quality of life.

Conclusion: We found no significant differences in cognition between the GBA related PD group and the matched GBA negative PD group, potentially because of early disease stages ($\bar{x}$ = 4.13 years) of the included patients, which is consistent with previous findings [3]. We will seek to complete these analyses with a more detailed neuropsychological assessment battery.

Additionally, we will perform longitudinal analyses to evaluate the effect of disease progression on the cognition in GBA PD carriers.

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INSIGHTS INTO THE IMPLEMENTATION OF A NATION-WIDE DEMENTIA PREVENTION PROGRAMME (pdp) IN LUXEMBOURG

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Objectives: The "programme démence prevention (*pdp*)" is a dementia prevention programme in Luxembourg, which uses personalised lifestyle interventions as a means to decelerate cognitive decline in individuals exhibiting a higher risk to develop dementia.

Background: Currently 55 million people are living worldwide with dementia and many more cases are expected to arise in the following years[1]. As there is no available cure at present, preventative measures may provide opportunities to alleviate social, economic, and psychological burden. Although initiatives have already been launched to identify modifiable dementia risk factors[2,3,4] and first studies underly the benefits of a multidomain approach to target such factors[5,6], it remains to be seen how to best implement such findings on a nation-wide level with an integrated care approach.

Methods: Treating physicians are invited to refer individuals with either a *subjective cognitive decline* (SCD) or a *mild cognitive impairment* (MCI) to the programme, where participants undergo a detailed neuropsychological evaluation as well as a personalized dementia risk factor profiling. Subsequently, an individualized action plan encompassing physical, cognitive, nutritional, and/or psychological interventions is established, and is cost-free through the distribution of vouchers. To discern potential changes in participants' cognitive status, risk profiles or health behaviours and to contingently adapt their action plans, a regular re-evaluation is scheduled.

Results: To date, 400 people have been screened for participation in *pdp*. The majority of these participants has learned about the programme through a treating physician (85,7%) while the rest has heard about the programme through other sources (friends, family, radio, etc). As far as the cognitive status of the participants is concerned, 89,2% present with an MCI and 5,5% present with an SCD. 4,8% display cognitive impairment with a loss of autonomy in their daily functioning. Thus, they can be classified as people with dementia. So far, 122 participants have been seen for a first follow-up visit, with preliminary findings revealing that 72% of them have followed up on at least one of their proposed lifestyle interventions. Dietary counselling (91,3%) as well as cognitive training in a group setting (83,8%) appear to be the most attractive voucher options.

Conclusion: Establishing a nation-wide programme, which aims to prevent dementia or at least to slow down cognitive decline within the Luxembourgish population, is feasible when involving both treating physicians as well as national partners which provide health care interventions targeting dementia risk factors. The experiences gathered by the programme may provide valuable insights how to incorporate preventive measures into national healthcare systems.

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MORE SMOKE THAN FIRE
NO SPEEDING UP OF PARKINSON'S DISEASE AFTER COVID-10 LOCKDOWN

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Background and objectives
As the influence of stress syndromes on the evolution of Parkinson's disease (PD) remains largely unexplored, the COVID-19 pandemic offers the opportunity to evaluate the stress impact of the COVID-19 pandemic on PD trajectories.
Methods
This longitudinal observational case-control study used data from the Luxembourg Parkinson's Study (1). A pandemic PD group with exposure to the restrictions imposed by the COVID-19 pandemic but without COVID-19 infection (n=79) was compared to a prepandemic PD control group (n= 117) that has never been exposed to any pandemic restrictions. All patients underwent three annual visits. The last analyzed in-person visit of the pandemic group occurred during the early pandemic phase, between September 2020 and March 2021. Motor and cognitive status were established through standardized in-person exams. Patients of the PD pandemic group self-rated their resilience and risk for posttraumatic stress disorder (PTSD) and, at visit 2 and 3, underwent the Olink panel of 92 serological inflammation markers. The primary outcome was motor PD progression as rated by the MDS-UPDRS part III score. The secondary outcomes were other progression scores (MDS-UPDRS I and II), cognitive performance (Montreal Cognitive Assessment), symptoms of depression (Beck Depression Inventory), risk for PTSD (revised Impact of Event Scale) and resilience (Brief Resilience Scale). Measures tested for statistical associations with these outcomes include demographic, lifestyle data and serological inflammation markers. To assess variable associations and correct effects from confounding factors, we used a multiple linear regression approach.
Results
The deterioration of the motor and cognitive scores from visit 1 to visit 3 was not different in the pandemic group compared to the prepandemic group. 74.7 % of the pandemic PD patients had normal or high resilience scores, whereas 20.3% were at risk of developing PTSD. Resilience was neither correlated with motor scores nor with cognitive scores but was negatively associated with depressive symptomatology and posttraumatic stress. Except for Axin-1, there was no increase in the inflammation markers at visit 3 compared to visit 2.
Discussion
This case-control study shows that there was no influence by the pandemic-induced stress on the natural progression of PD motor and cognitive trajectories.

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VISUAL DYSFUNCTION IN PARKINSON'S DISEASE GBA CARRIERS: AN EXPLORATORY ANALYSIS

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Objective: In this exploratory analysis, our aim was to identify potential differences in the visuo-perceptual performances in Parkinson's disease (PD) patients with and without glucocerebrosidase (GBA) variants and in non-affected controls with and without GBA variants.
Background: It is well known that non-motor symptoms are frequent in Parkinson's Disease (PD), including visuo-perceptive features[1]. These latter consist of changes in contrast sensitivity, colour discrimination and face emotion recognition, especially in negative emotions[2]. GBA mutations decrease the cerebral blood flow in the parietal lobe and the precuneus[2], areas involved in visuo-perceptual tasks[3]. To our knowledge, only one study showed that colour discrimination might be increased in GBA PD patients compared to patients without known GBA variants[4].
Methods: Patients with idiopathic PD and controls were recruited from the Luxembourg Parkinson's Study with mandatory basic clinical assessments as well as optional visual assessments[5]. Depending on results from deep-sequencing of the whole GBA locus via PacBIO technology, participants were divided into patients with GBA variants (PD-GBA+), patients without GBA variants (PD-GBA -), non-affected controls with GBA (Control-GBA+) and without GBA (Control-GBA-). The PD-GBA+ was composed of 5 low-risk variants, 2 severe and 1 mild, whereas the Control-GBA+ was only composed of low-risk variants. Both groups were matched for age and gender and the patient group additionally for disease duration. Several visuo-perceptual tests including the *Farnsworth Munsell 100 Hue Test (FM100)*[6] and the *Kybervision Contrast sensitivity*[7] were performed to assess colour discrimination and contrast sensitivity, respectively. The *Ekman 60 Faces Test*[8] was used to evaluate the recognition of facial expressions of the 6 basic emotions (anger, disgust, happiness, fear, sadness and surprise). First, we compared the visuo-perceptual performances between the two control groups and in a second step the same performances in the patient's groups.
Results: 16 patients (8 PD-GBA+ and 8 PD-GBA-) and **10 controls** (5 controls GBA+ and 5 controls GBA-) were included in the statistical analyses. After multiple testing correction, we found that the PD-GBA+ group had significantly lower scores in the Ekman 60 Faces test especially for the emotion surprise compared to their matched counterpart ($p = 0.026$). However, no significant differences in global cognition nor in the other visuo-perceptual performances were found in the patient groups. Additionally, the control groups did not significantly differ in any of the investigated variables.

Conclusion: Our results suggest specific differences for PD patients in the sub-item emotion of the Ekman 60 Faces Test depending on their GBA carrier status. As surprise bilaterally activates the inferior frontal gyrus and the hippocampus[10], it would be of interest to investigate whether a higher alpha-synuclein burden exists in these specific regions. Additionally, we will investigate whether the absence of significant differences between the groups was the result of the small sample size.

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IS IT ALL ABOUT SUBJECTIVE COGNITIVE COMPLAINT? A PRELIMINARY ANALYSIS IN A LUXEMBOURGISH PARKINSON'S DISEASE COHORT

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Objective: This study sought to investigate subjective cognitive complaint (SCC) in patients with idiopathic Parkinson's Disease (IPD) and its relation to objective cognitive deficits (OCD).
Background: Cognitive symptoms are frequently seen in PD patients but were underestimated for a long time, although it is one of the most disabling features of the disease[1]. The concept of SCC has gained a growing interest in the last few years due to its potential ability for earlier detection of cognitive decline[2]. SCC is known as the self-reported experience of worsening of cognitive functions, while the results on neuropsychological tests remain normal compared to age-, sex- and education-adjusted normative data[2].
Methods: Patients with IPD were recruited from the Luxembourg Parkinson's Study[3]. We created a composite score for SCC by using the items 31 and 32 of the PDQ-39 questionnaire. We defined a total score of > 3 as SCC (SCC+ group). Our exclusion criteria entailed patients with other neurological diseases and patients with an existing Mild Cognitive Impairment (MCI), as defined by a total score <26 by the Montreal Cognitive Assessment (MoCA)[6]. Both groups were matched for age, years of education and disease duration. The MoCA total score and the total number of words produced within one minute (phonemic fluency task) were used to evaluate the OCD. The Beck Depression Inventory (BDI-I) and the Starkstein Apathy Scale (SAS) were included to measure depressive symptoms and apathy, respectively. The feeling of well-being of our patients was measured by the subscore "well-being" of the PDQ-39 (item 17 – 22) with a possible total score of 24.
Results: A total of 134 patients (67 SCC+ and 67 SCC-) were included with a mean age of 63.37 (SD = 9.99) and 63.27 years (SD = 9.63) and mean disease duration of 5.12 (SD = 4.88) and 3.94 years (SD = 4.65) respectively. The years of education were 14.16 (SD = 3.67) for the SCC+ group and 14.22 (SD = 3.48) for the SCC-. After correcting for multiple testing, the SCC+ group showed higher depressive symptoms (13.31 versus 4.46, p <0.001), higher apathy scores (14.95 versus 10.54, p < 0.001) and higher emotional burden (9.50 versus 1.64, p < 0.001). Interestingly, the SCC+ group also produced significantly less words in the phonemic fluency task (10.65 versus 11.92, p = 0.032), whereas the MoCA total score did not significantly differ between both groups (p = 0.99).
Conclusion: Our results showed that patients reporting a SCC according to our composite score have higher emotional burden than those without SCC, although the MoCA scores did not differ significantly between both groups. These results are consistent with previous findings[5] showing that greater negative affective burden was associated with lower self-perceived cognitive functioning. We aim to further investigate SCC in longitudinal analyses, including more detailed

neuropsychological tests as well to investigate whether SCC could be an early predictive marker of OCD.

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STRATEGY TO INVESTIGATE THE PROGRESSION OF COGNITIVE DECLINE IN THE LONGITUDINAL LUXEMBOURG PARKINSON'S STUDY

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Cognitive impairment is one of the most prevalent non-motor symptoms in Parkinson's disease (PD). Approximately 20% to 33% of PD patients already present with mild cognitive impairment (MCI) at the time of PD diagnosis, and up to 80% develop dementia within 20 years after disease onset. MCI is a known risk factor for the development of dementia and is associated with increased mortality. Therefore, it is important to predict the rate of cognitive decline in the early stages of the disease, thus allowing clinicians to better personalize and tailor patient's treatment. The goal of this project is to identify the characteristics of PD patients converting from a) normal cognition to MCI, and b) from MCI to dementia by making use of the multimodal data derived from the longitudinal Luxembourg Parkinson's Study. Additionally, we aim to (i) identify key predictors of disease progression, (ii) to estimate cognitive decline rates within the PD population, and (iii) to use data-driven individualization approaches. The longitudinal data collected within the Luxembourg Parkinson's Study includes standardized clinical tests, global cognitive data, as well as genetic, omics and medication data. Moreover, two levels of neuropsychological assessments are offered to each participant: level A, based on basic cognitive assessments and mandatory for all the patients, whereas level B is optional and a rather detailed neuropsychological evaluation focusing on specific cognitive domains. An exhaustive review comparing the different neuropsychological tests available in the Luxembourg Parkinson's Study dataset with the related literature was conducted and resulted in a total of 36 identified tests relevant for the definition of MCI and dementia, according to the Movement Disorder Society criteria. Thus, the PD population of the Luxembourg Parkinson's study will be longitudinally stratified into PD without cognitive impairment, MCI and dementia. A preliminary descriptive analysis of the characteristics of these different subgroups will be presented during the conference.

DEVELOPMENT OF AN EVALUATION FRAMEWORK FOR DIGITALLY ENABLED INTEGRATED CARE: CONNECTED CARE PD

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Abstract

Background: Digital health is increasingly recognized as a major driver of quality in healthcare by offering scalable tools to improve health, healthcare delivery, as well as supporting integrated care networks. Digitalisation in medicine also generates a large volume of real-world healthcare data that offers the potential for new ways of measuring health and consequently providing personalised care and precision medicine. However, the wider implementation of digitally enabled integrated care models depends on the provision of credible evidence on their health effectiveness, cost-effectiveness and the adoption of digital technologies by patients and healthcare professionals. Thus, in this study we outline an evaluation framework by providing a standard set of indicators that incorporate both medical and socioeconomic dimensions along a patient's journey. We use the Connected Care PD (Parkinson Disease) programme in Luxembourg as a case study of an integrated and multidisciplinary environment where currently digital solutions are being implemented in order to monitor and evaluate patient health and healthcare performance.

Methods: To arrive at this first set of standardized and patient-centred indicators, we first looked at the established set of guidelines and standards in the literature. Next, we used a consensus driven method by engaging different experts from the Parkinson disease field such as health professionals and academics from different backgrounds (medicine, social science and health economics). Patients' voices will also be included in defining the final set of outcomes.

Results: We provide a comprehensive list of medical and socioeconomic indicators that can be used to monitor healthcare quality for people with Parkinson disease, identify potential sources, and highlight current challenges in the healthcare system that impede the integrated collection of healthcare data. We recommend practical ways of designing efficient and timely ways of collecting healthcare data through an integrated system of healthcare claims-based data, electronic health records and patient relevant outcomes (PROMs/PREMs). In the future these sources could be supplemented by wearable devices and patient apps. Such integrated data sources based on real world data are vital for identifying the delivery of precision health and evaluating digitally enabled healthcare interventions.

THE NEUROPSYCHOLOGICAL PROFILE AND OTHER CLINICAL CHARACTERISTICS IN NON-AFFECTED GBA-CARRIERS VERSUS HEALTHY NON-CARRIERS

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Objective: This study aimed to investigate the cognitive functioning of at-risk individuals for Parkinson's Disease (PD), by comparing the neuropsychological profile and other clinical characteristics in non-affected glucocerebrosidase (GBA) carriers versus healthy non-carriers.
Background: Variants in the GBA gene are the most common genetic risk factor for PD. Non-affected GBA carriers (NAC-GBA) could provide an insight into the prodromal cognitive functioning of those at risk of developing PD, although most of them do not develop PD due to low penetrance. Studies investigating cognition in GBA carriers show some incongruent results that may be due to differences in methodology, such as sample sizes, variety of mutation types, assessment instruments as well as polymorphism (1,2, 3), thereby warranting further research.
Methods: Data was used from the Luxembourg Parkinson's Study (1), to compare a non-affected GBA carrier (NAC-GBA) group to a control group without any known mutation(s). Demographic data and neuropsychological results have been collected. More details on the neuropsychological tests used have been published elsewhere (see level A and the optional level B)[3]. Furthermore, the following questionnaires were included in the analyses: Beck Depression Inventory (BDI-I), Starkstein Apathy Scale, SCales for Outcomes in PArkinson's Disease-Autonomic questionnaire (Scopa-Aut), REM Sleep Behaviour Disorder Screening Questionnaire, MDS-UPDRS I-III and the Parkinson's Disease Quality of Life Questionnaire (PDQ-39), to assess symptoms of depression, apathy, autonomic features, REM Sleep behavior disorder, motor and non-motor PD aspects, respectively.
Results: After the exclusion of participants with manifest Parkinsonism and other neurological comorbidities, 28 participants were included in total: 14 NAC-GBA (12 with low-risk, 1 with mild risk and 1 with severe risk) and 14 age -, sex and years of education - matched control subjects. The mean age was 58.9 years (SD = 15.27) for the NAC-GBA group and 58.05 years (SD = 15.32) for the control group. Our results displayed that the NAC-GBA group performed significantly worse on the episodic memory delayed recall test (CERAD Word List Memory) than the healthy non-carriers group (7.9 versus 6.5 out of 10, SD = 1.90 versus SD = 1.95, $p_{corrected} = 0.04$), whereas non-significant differences were found in the other neuropsychological tests, as well as in the motor and other non-motor symptoms.
Conclusion:
In our preliminary analyses, the delayed recall scores in the episodic memory differed significantly between both groups, with the NAC-GBA group performing worse than the healthy non-carriers group.

However, both groups performed similarly on the rest of the neuropsychological tests; thereby our results indicate no difference in global cognitive performance between the NAC-GBA and healthy non-carriers. Additionally, both groups showed similar results in terms of quality of life, motor and other non-motor symptoms. Importantly, our results need to be interpreted with caution, given the reduced sample size and the high proportion of low-risk mutations among the NAC-GBA. We will conduct a longitudinal analysis to gain a deeper understanding of the neuropsychological profile and clinical characteristics of NAC-GBA, as well as to evaluate the evolution of the prodromal features of PD.

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