Third «pHysiopathology Of Parkinson's disEase » (HOPE) Meeting

Bordeaux, January 29-31, 2025

Program:

DAY 0 January 29

18h30-20h00 (Amphithéâtre Pôle juridique et judiciaire (PJJ))
Talk Grand public (in French, evening) : "Parkinson lève le voile sur la dopamine"
Pr. David Devos, Neurologist and Professor in Medical Pharmacology (Lille, France)

DAY 1 January 30

MORNING
8h15-8h30: Opening of the conference
Welcoming of the congress - Welcoming of Participants - Organization committee and NeurATRIS: Dr. Philippe Hantraye (MIRCen, Fontenay aux Roses, France)

Session 1: Physiopathology (Chairs: Elaine Del Bel & Agnès Chaperon)
1) 8h30-9h00: Cortical somatostatin interneurons as a (potential) therapeutic target in Parkinson's disease
Laurent Venance (Paris, France)
2) 9h00-9h30: Functions of the external globus pallidus in motor control in health and Parkinson's disease
Jerôme Baufreton (Bordeaux, France)
3) 9h30-9h50: 2 Flash talks
9h30-9h40: Deciphering Impulse Control Disorders mechanisms related to dopamine agonists in PINK1-related Parkinson's Disease Assunta Pelosi (Paris, France)
9h40-9h50: The role of the Locus Coeruleus-Hippocampus pathway in the early phases of Parkinson's disease Laura De las Heras-García (Leioa, Spain)

9h50-10h20: Coffee Break

Session 2: Imaging (Chairs: Philippe Hantraye & Anna Lovisotto)
1) 10h20-10h50: Parkinson's disease and multiple system atrophy: the usefulness of clinical biomarkers and neuroimaging
Margherita Fabbri (Toulouse, France)
2) 10h50-11h20: Neuromelanin-sensitive MRI: a biomarker of substantia nigra degeneration in Parkinson's disease
Stéphane Lehéricy (Paris, France)
3) 11h20-11h30: 1 Flash talk

11h20-11h30: In vivo targeting alpha-synuclein fibrils by specific nanobody in mice Claire Mazzocco (Bordeaux, France)

Session 3: Patients and associations
1) 11h30-11h40 : Patient's testimony
2) 11h40-11h50 : Marie Fuzzati **- Association France Parkinson**
3) 11h50-12h00 : Marion Lévy **- Fondation Vaincre Alzheimer**

12h00-14h00: Lunch – Discussion – Networking + poster session (13h-14h)

AFTERNOON
Session 4: Synucleinopathy Part I (Chairs: Peter Vangheluwe & Emma Perrot)
1) 14h00-14h30: Understanding multiple system atrophy pathogenesis: from amyloid structure to brain pathology and the other way around
Florent Laferrière (Bordeaux, France)
2) 14h30-15h00: Functional and neuropathological changes induced by distinct alpha-synuclein strains
Romina Aron Badin (Fontenay aux Roses, France)
3) 15h00-15h30: Alpha-synuclein in the brain and digestive tract: the same battle?
Pascal Derkinderen (Nantes, France)
4) 15h30-15h50: 2 Flash talks
15h30-15h40: Distinct Tau Pathology Profiles Induced by Distinct Parkinson Patient-derived Alpha-Synuclein Aggregates in Non-Human Primates Morgane Darricau (Bordeaux, France)
15h40-15h50: The Chaperone DNAJB6 Inhibits alpha-synuclein Aggregation in Models of Induced Synucleinopathy Aenora Letourneur (Bordeaux, France)

15h50-16h20: Coffee Break

Session 4: Synucleinopathy Part II (Chairs: Solange Desagher & Ludivine Sabatier)
1) 16h20-16h50: Unraveling the role of alpha-synuclein aggregation in Parkinson's disease and related disorders
Veerle Baekelandt (Leuven, Belgium)
2) 16h50-17h20: The role of periventricular microglia in Parkinson´s disease.
Isabel Fariñas (Valencia, Spain)
4) 17h20-17h40: 2 Flash talks
17h20-17h30: Human TFEB overexpression prevents mutant human A53T–α-synuclein toxicity in a prevention design applied to a rat model of Parkinson's disease Marie-Laure Arotçarena (Bordeaux, France)
17h30-17h40: Investigating early mechanisms of alpha-synuclein pathology in iPSC-derived midbrain organoids Federico Bertoli (Paris, France)

DAY 2 January 31

MORNING
8h15-8h30 Welcoming

Session 5: Genetics and Environment (Chairs: Christelle Tesson & Helena Winterberg)
1) 8h30-9h00: Monogenic forms of Parkinson's disease: from genes to precision medicine
Alexis Brice (Paris, France)
2) 9h00-9h30: Environmental, Genetics and PD
Alexis Elbaz (Paris, France)
3) 9h30-9h50: 2 Flash talks
9h30-9h40: RFC1 expansions: a rare cause of parkinsonism Violette Delforge (Lille, France)
9h40-9h50: Use of long-read whole genome sequencing to solve exome-negative early-onset and familial Parkinson's disease cases Guillaume Cogan (Paris, France)

9h50-10h20: Coffee Break

<u>Session 6:</u> Organelles (Chairs: Patrick Michel & Jakob Scharnholz)
1) 10h20-10h50: ATP13A2 in Parkinson's disease: Implications of disturbed lysosomal polyamine transport Peter Vangheluwe (Leuven, Belgium)
2) 10h50-11h20: Mitochondria-Lysosomes crosstalk in Parkinson's disease: a role for alpha-synuclein Marisa Brini (Padoue, Italy)
3) 11h20-11h40: 2 Flash talks
11h20-11h30: Phenotypic characterization of an ATP13A2 knockout rat model of Parkinson's disease Rémi Kinet (Bordeaux, France)
11h30-11h40: Assessing Modulation of LRRK2:14-3-3 interaction on Parkinson's Disease-associated cellular phenotypes Margaux Morez (Lille, France)

<u>Session 7:</u> Translational Development Part I (Chairs: Alexis Brice & Léa Bonamy)
1) 11h40-12h10 Dyskinesia and protection in preclinical models of Parkinson's disease
Elaine Del Bel (Sao Paulo, Brazil)
2) 12h10-12h40 Towards brain-controlled therapies of brain and spinal cord to alleviate deficits of gait and balance in Parkinson's patients
Eduardo Martin Moraud (Lausanne, Switzerland)
3) 12h40-12h50: 1 Flash talk
12h40-12h50: Urinary proteome profiling in rats and humans unveils biomarkers of LRRK2 kinase activity in Parkinson's disease Jean-Marc Taymans (Lille, France)

12h50 - 13h00 Best poster presentation award

13h00 - 14h00 Lunch - Discussion - Networking and Picture (13h50-14h00)

AFTERNOON
<u>Session 7:</u> Translational Development Part II (Chairs: Isabel Fariñas & Juan Estaun-Panzano)
1) 14h00 - 14h30 GLP-1 receptor agonists for treating PD and MSA
Wassilios Meissner (Bordeaux, France)
2) 14h30 - 15h00 A metabolic biomarker for an improved diagnosis of Parkinson's disease
Sabrina Boulet (Grenoble, France)
3) 15h00-15h10: 1 Flash talk
15h00-15h10: The Pyruvate Dehydrogenase as a new potential therapeutic target in Parkinson's disease pathophysiology Vanille Millasseau (Grenoble, France)

<u>Session 8:</u> Stem cells and OMICS (Chairs: Florent Laferrière & Hugo Jadot)
1) 15h10 - 15h40 Assembling region-specific human brain organoids to model Parkinson's disease
Philippe Ravassard (Paris, France)
2) 15h40- 16h10 NeuroImmune Interactions in Stem Cells
Michela Deleidi (Paris, France)
3) 16h10 – 16h20: 1 Flash talk
16h10 – 16h20: Dissecting the role of LRRK2 in intercellular communication using iPSC-derived neuron-glia tricultures Carmela Giachino (Paris, France)

4) 16h20 – 16h30: Best oral presentation and Conclusions

POSTER

N°	Nom	Prénom	Titre
1	Pelosi	Assunta	Deciphering Impulse Control Disorders mechanisms related to dopamine agonists in PINK1-related Parkinson's Disease
2	De Las Heras-Garcia	Laura	The role of the Locus Coeruleus-Hippocampus pathway in the early phases of Parkinson's disease
3	Darricau	Morgane	Additive effect of distant Lewy bodies and tau seeds injections on nigral degeneration in macaques
4	Darricau	Morgane	Distinct Tau Pathology Profiles Induced by Distinct Parkinson patient-derived Alpha-Synuclein Aggregates in Non-Human Primates
5	Lovisotto	Anna	Understanding Extracellular Diffusion in Multiple System Atrophy Mouse Model
6	Kinet	Rémi	Phenotypic characterization of an ATP13A2 knockout rat model of Parkinson's disease
7	Kinet	Rémi	Differential Pathological Dynamics triggered by distinct Parkinson patient-derived α-synuclein extracts in non-human primates
8	Mazzocco	Claire	In vivo targeting alpha-synuclein fibrils by specific nanobody in mice
9	Scharnholz	Jakob	Dopaminergic physiology in the substantia nigra pars compacta of recombinant a-synuclein pre-formed fibrils injected mice
10	Perrot	Emma	Exploring Motor and Non-Motor Symptom Progression in a Synucleinopathy Mouse Model of Parkinson's Disease
11	Arotçarena	Marie-Laure	Harnessing chaperone-mediated autophagy through viral- based LAMP2A overexpression in the Lewy body-injection non-human primate model of Parkinson's Disease

12	Arotçarena	Marie-Laure	Human TFEB overexpression prevents mutant human A53T–α-synuclein toxicity in a prevention design applied to a rat model of Parkinson’s disease
13	Giachino	Carmela	Dissecting the role of LRRK2 in intercellular communication using iPSC-derived neuron-glia tricultures
14	Bertoli	Federico	Investigating early mechanisms of alpha-synuclein pathology in iPSC-derived midbrain organoids
15	Sabatier	Ludivine	Monitoring α-synuclein seeding and discrimination of amyloids amplified in vitro from biological samples
16	Akhmedullin	Ruslan	Antiepileptic Drugs and Parkinson's Disease: A Meta-Analysis of Existing Evidence
17	Brachet	Guillaume	A combination of antidiabetics achieves neuroprotection in a cellular model of Parkinson's disease
18	Cogan	Guillaume	Use of long-read whole genome sequencing to solve exome negative early-onset and familial Parkinson’s disease cases
19	Delforge	Violette	RFC1 EXPANSIONS: A RARE CAUSE OF PARKINSONISM
20	Millasseau	Vanille	The Pyruvate Dehydrogenase as a new potential therapeutic target in Parkinson’s disease pathophysiology
21	Morez	Margaux	Assessing Modulation of LRRK2:14-3-3 interaction on Parkinson’s Disease-associated cellular phenotypes
22	Jadot	Hugo	Nanovectors for lysosome-based therapeutic strategies against neurodegenerative diseases
23	Bonamy	Léa	Role of Arkypallidal neurons in motor symptoms of Parkinson’s Disease and Levodopa-Induced Dyskinesia
24	Tesson	Christelle	Identification of new candidate genes involved in autosomal recessive forms of Parkinson’s disease
25	Letourneur	Aenora	The Chaperone DNAJB6 Inhibits aSyn Aggregation in Models of Induced Synucleinopathy
26	Winterberg	Helena	Microglia-enriched human midbrain organoids for studying Parkinson’s disease
27	Taymans	Jean-Marc	Urinary proteome profiling in rats and humans unveils biomarkers of LRRK2 kinase activity in Parkinson's disease
28	Chaperon	Agnés	Glucocorticoid receptors in astrocytes regulate alpha-synuclein pathological actions impacting motor and non-motor symptomology of Parkinson's disease.
29	Lassot	Iréna	Transcriptional Regulation of α-synuclein Expression by TRIM17/TRIM41/ZSCAN21 pathway in Parkinson’s disease

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3RD THIRD «PHYSIOPATHOLOGY OF PARKINSON'S DISEASE » (HOPE) MEETING BORDEAUX, JANUARY 29-31, 2025

Deciphering Impulse Control Disorders mechanisms related to dopamine agonists in PINK1-related Parkinson's Disease

Assunta Pelosi[1], Marie Braun[1], Lisa Sonam[1], Corentin Catté[1], Eglantine Allain[1], Sophie Longueville[2], Denis Hervé[2], Jean-Antoine Girault[1,2], Olga Corti[1], Jean-Christophe Corvol[1], Louise-Laure Mariani[1,2]

1) Molecular Pathophysiology of Parkinson's Disease, Paris Brain Institute/CNRS UMR 7225/INSERM U 1127/Sorbonne University;

2) Neurotransmission and Signaling, Institut du Fer à Moulin, INSERM UMR-S 1270, Sorbonne University, Paris, France

Impulse control disorders (ICDs) are frequent and severe complications in patients with Parkinson's disease (PD). They are characterized by the inability to resist the urge or impulse of a usual and pleasurable activity. The main risk factor is the use of dopamine agonists (DAs). Genetic factors are also suspected. In Parkinsonian patients carrying a mutated Parkin, ICDs have a greater frequence and severity. Although, ICDs are a severe clinical problem, their pathophysiology is still not well understood and experimental models appear to be needed. Here we present the results of the effects of a chronic treatment (4 weeks with 0,5 mg/kg) with the DA agonist pramipexole (PPX) in wild-type and Parkin-KO mice. Results of the Variable Delay Signal test conducted in these mice did not show any sign of impulsivity calculated as number of premature and perseverative responses when compared with control animals (saline). However, the latency to respond and the number of omissions were significantly increased in the PPX group compared to controls for both wild-type and Parkin-KO mice. PPX treatment also increased locomotion and off-platform intrusion in the Cliff Avoidance Reaction, which is a sign of impulsivity, with higher effect in Parkin-KO mice compared to the wild-type. These results suggest that DAs treatment activates pathways involved in impulsive behaviors and validate the impulsivity tests for future studies on parkinsonian mouse models.

Assunta Pelosi (assunta.pelosi@icm-institute.org).

After my PhD in molecular microbiology, I shifted my research interest on the nervous system with a first Post-doctoral training at Medical Center of the Johannes Gutenberg University in Mainz in of Prof. Robert Nitsch's lab working on the role of the post-synaptic protein plasticity-related-gene-1 (PRG-1) on the hippocampus circuit during development. Then, I focused my research on the study of the Basal Ganglia circuit and the implications of maladaptive striatal signaling in the development of L-dopa-induced dyskinesia and more recently on the development of impulsive compulsive disorders using rodent parkinsonian models.

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Abstract should be one page max (all texts and references). No Figure.

During my career I have also worked at Sanofi's Neuroscience R&D and trained many students in academia. I am currently balancing fundamental research projects with clinical projects working as deputy CSO at Neurotrials, a CRO-like structure within the Paris Brain Institute and as a researcher in the Molecular Pathophysiology Parkinson's disease team.

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Abstract should be one page max (all texts and references). No Figure.

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3RD THIRD «PHYSIOPATHOLOGY OF PARKINSON'S DISEASE » (HOPE) MEETING BORDEAUX, JANUARY 29-31, 2025

The role of the Locus Coeruleus-Hippocampus pathway in the early phases of Parkinson's disease.

Laura De las Heras-García [1,2,3], Jone Razquin[1, 3], Celtia Domínguez-Fernández [4], Edgar Soria-Gómez [5, 6], Jose Ángel Ruiz-Ortega[1], Gloria González-Aseguinolaza[7], Jérôme Baufreton[2], Cristina Miguélez-Palomo[1, 3]

1) *Department of Pharmacology, Faculty of Medicine and Nursing, Univ. Basque Country UPV/EHU, E-48940, Leioa, Spain.*
2) *Univ. Bordeaux, CNRS, IMN, UMR 5293, F-33000 Bordeaux, France.*
3) *Neurodegenerative diseases Group, Instituto de Investigación Sanitaria Biobizkaia, Hospital Universitario de Cruces, E-48903, Barakaldo, Spain.*
4) *Research and Development Division, IMG Pharma Biotech, 48160 Derio, Spain.*
5) *Achucarro Basque Center for Neuroscience, Univ. Basque Country UPV/EHU, E-48940, Leioa, Spain.*
6) *IKERBASQUE, Basque Foundation for Science, Bilbao, Spain.*

Although Parkinson's disease (PD) is becoming increasingly important in ageing societies, its diagnosis still relies on the presence of classical motor symptoms that usually only manifest in the later stages of the disease's progression. Patients may, however, present non-motor signs as cognitive and/or mood issues years prior to the onset of the motor ones[1,2]. The Locus Coeruleus (LC) is one of the first areas to exhibit Lewy bodies and neurodegeneration. Its dysfunction is associated to the appearance of nonmotor symptoms due to its noradrenergic (NA) projections and influence on the homeostasis of dopaminergic (DA) networks [3,4,5]. We have set up a prodromal mouse model of human α-syn overexpression at the LC by viral vector stereotaxic injections. Our goal is to characterize behavioural, functional, and structural changes driven by dysregulation of the LC-NA system, locally and in projecting areas such as the hippocampus, amygdala, or prefrontal cortex. Thus, we have studied behavioural phenotypes finding affectations related to spatial, working, and aversive memories. Moreover, we have analysed structural changes in local inflammatory-related cells, as astrocytes and microglia, together with alterations in NA fibre network. These data, along with preliminary functional studies, provide an insight into how LC-NA dysregulation occurs at very early phases of PD and may aid in the search for early markers to facilitate its diagnosis.

1. Blesa, J., Foffani, G., Dehay, B., Bezard, E. & Obeso, J. A. Motor and non-motor circuit disturbances in early Parkinson disease: which happens first? *Nature Reviews Neuroscience* vol. **23** 115–128 at https://doi.org/10.1038/s41583-021-00542-9 (2022).
2. Paredes-Rodriguez, E., Vegas-Suarez, S., Morera-Herreras, T., De Deurwaerdere, P. & Miguelez, C. The Noradrenergic System in Parkinson's Disease. *Frontiers in Pharmacology* vol. **11** at https://doi.org/10.3389/fphar.2020.00435 (2020).
3. Ray Chaudhuri, K., Leta, V., Bannister, K., Brooks, D. J. & Svenningsson, P. The noradrenergic subtype of Parkinson disease: from animal models to clinical practice. *Nature Reviews Neurology* vol. **19** 333–345 at https://doi.org/10.1038/s41582-023-00802-5 (2023).
4. Oertel, W. H., Henrich, M. T., Janzen, A. & Geibl, F. F. The locus coeruleus: Another vulnerability target in Parkinson's disease. *Mov. Disord.* **34**, 1423–1429 (2019).
5. Braak, H. et al. Staging of Brain Pathology Related to Sporadic Parkinson's Disease. *Neurobiology of Aging* vol. **24** (2003).

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3RD THIRD «PHYSIOPATHOLOGY OF PARKINSON'S DISEASE » (HOPE) MEETING BORDEAUX, JANUARY 29-31, 2025

Laura De las Heras-García

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PERSONAL INFORMATION
Date of birth: 30/12/1997
Place of birth: Aranda de Duero (Burgos, Spain)

I am a biomedical scientist with a Master's degree in neuroscience. Currently, I am pursuing my PhD on noradrenergic circuit dysfunction in early Parkinson's stages under the supervision of Dr. Cristina Miguélez (UPV/EHU) and Jérôme Baufreton (UB). Additionally, I have expertise in foundations of scientific culture and I balance my lab. work with social media and communication activities for both children and adults.

EDUCATION

(2022-2026) **Neurosciences PhD Programme** - **Pharmacology PhD Programme**
Université de Bordeaux (UB), Universidad del País Vasco (UVP/EHU)

(2022-2023) **Postgraduate certificate in Culture and Philosophy of Science**
Universidad Pública de Navarra – UVP/EHU

(2020-2021) **MSc in Neurosciences**
UVP/EHU

(2016-2020) **BSc in Biomedical Sciences**
Universitat de Barcelona

LABORATORY EXPERIENCE

(2022-2026) **PhD Candidate (Neuroscience and Pharmacology, co-tutelled programme)**
Dopamine et assemblées neuronales Lab. (IMN-UB)
Neuropharmacology Lab. (UPV/EHU)

(2020-2022) **Master Thesis and Intern researcher**
Laboratory of glial and neuronal autophagy (Achucarro BCN, UPV/EHU)

(2020) **Bachelor Thesis**
Parkinson's disease and other neurodegenerative movement disorders Lab. (IDIBAPS, Hospital Clínic de Barcelona)

PUBLICATIONS

Egiguren-Ortiz, J., Domínguez-Fernández, C., Razquin, J., De las Heras-García, L., et al. (2024) Reactive antibodies against brain antigens as serological biomarkers of neurodegenerative diseases. *Advanced Neurology* 3(1), 2058. https://doi.org/10.36922/an.2058

Domínguez-Fernández, C., Egiguren-Ortiz, J., Razquin, J., Gómez-Galán, M., De las Heras-García, L., et al. (2023). Review of Technological Challenges in Personalised Medicine and Early Diagnosis of Neurodegenerative Disorders. *International Journal of Molecular Sciences*, 24(4), 3321. MDPI AG. http://dx.doi.org/10.3390/ijms24043321

Beccari, S., Sierra-Torre, V., Valero, J., Pereira-Iglesias, M., García-Zaballa, M., Soria, F. N., De Las Heras-Garcia, L., et al. (2023). Microglial phagocytosis dysfunction in stroke is driven by energy depletion and induction of autophagy. *Autophagy*, 1–30. https://doi.org/10.1080/15548627.2023.2165313

De las Heras-García, L., Zabalegui, I. & Pampliega, O. (2023) Methods to study primary cilia and autophagy in the brain. Academic Press. https://doi.org/10.1016/bs.mcb.2023.01.010

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3RD THIRD «PHYSIOPATHOLOGY OF PARKINSON'S DISEASE » (HOPE) MEETING BORDEAUX, JANUARY 29-31, 2025

Additive effect of distant Lewy bodies and tau seeds injections on nigral degeneration in macaques

Morgane Darricau[1], Valentine Kulifaj[1,2], Qin Li[3], William A. McEwan[4], Maria Xilouri[5], Benjamin Dehay[1], Erwan Bezard[1,6,#] and Vincent Planche[1,7,#]

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6. Motac Neuroscience Ltd, Bordeaux, France ;
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In neurodegenerative diseases, co-pathologies' influence on the emergence of a clinical phenotype is increasingly acknowledged. Recently, it has been suggested that nigral tauopathy may contribute to the nigrostriatal degeneration characterizing Parkinson's disease (PD) and Parkinsonism, either independently or in conjunction with Lewy body (LB) pathology. However, these conclusions are primarily based on post-mortem neuropathological correlations, and there is (yet) no direct experimental evidence to support this hypothesis. Here, we study the neuropathological impact of spreading these two proteinopathies toward the mesencephalon by injecting macaques (*Macaca mulatta*) with LB, tau aggregates, and a combination of LB and Tau aggregates.

PD brain-derived LBs (PD-LB) were injected into the striatum of seven macaques. Alzheimer's disease (AD) brain-derived tau seeds (AD-tau) were injected into the thalamus, located above the mesencephalon, in four macaques. A third group of four macaques received the combination of PD-LB into the striatum and AD-tau into the thalamus. We injected tau extracts from aged-matched healthy brains in three macaques, as a control procedure.

Eighteen months post-surgery, we observed increased mesencephalic staining of pS129 α-synuclein in macaques injected with LB, tau, or LB+tau. We found mesencephalic AT8-positive phosphorylated tau in macaques injected with tau or LB+tau. The stereological counting of nigral tyrosine-hydroxylase-positive neurons showed a significant neuronal loss in macaques injected with LB (-26.5%), tau seeds (-38.4%), or LB+tau (-53.5%).

Our findings support that nigral dopaminergic neuronal death can be caused by the spreading of tau proteopathic seeds and α-synuclein-containing LB from rostral connected regions, with a cumulative effect of the co-pathology. Further investigations will aim to characterize the presence of tauopathy and synucleinopathy across various brain regions.

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HOPE2025

3RD THIRD «PHYSIOPATHOLOGY OF PARKINSON'S DISEASE » (HOPE) MEETING BORDEAUX, JANUARY 29-31, 2025

Morgane Darricau (morgane.darricau@u-bordeaux.fr)

I studied Biology at the University of Bordeaux, where I earned a Master's degree in Nutrition and Food Science. During my internship at the NutriNeuro lab, I investigated the effects of vitamin A deficiency and supplementation on the nigrostriatal system in rat models of Parkinsonism.
I then completed a PhD at the Institute of Neurodegenerative Disease in Dr. Erwan Bezard's team, focusing on tauopathies in non-human primates under the supervision of Dr. Vincent Planche. My research primarily involved immunohistochemistry and biochemistry techniques applied to non-human primate tissues.
Currently, I am a postdoctoral researcher, advancing my work on understanding and modeling these disorders.

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Distinct Tau Pathology Profiles Induced by Distinct Parkinson patient-derived Alpha-Synuclein Aggregates in Non-Human Primates

Morgane Darricau[1], Camille Neu-Faber[2], Mathieu Bourdenx[3], Sandra Dovero[1], Gregory Porras[4], Marie-Laure Thiolat[1], , Ines Trigo-Damas[5,6], Cristina Estrada[7,8], Nuria Garcia-Carrillo[9], Maria Trinidad Herrero[7,8], Miquel Vil[6,10 11, 12,13], Jose A Obeso[5,6,13,14], Vincent Planche[1,15], Erwan Bezard[1,4,#] and Benjamin Dehay[1,#]

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8. Institute of Research on Aging (IUIE), School of Medicine, University of Murcia, 30100 Murcia, Spain;
9. Centro Experimental en Investigaciones Biomédica (CEIB), Universidad de Murcia, Murcia, Spain;
10. Neurodegenerative Diseases Research Group, Vall d'Hebron Research Institute (VHIR), Barcelona, Spain;
11. Department of Biochemistry and Molecular Biology, Autonomous University of Barcelona (UAB), Barcelona, Spain;
12. Catalan Institution for Research and Advanced Studies (ICREA), Barcelona, Spain;
13. Aligning Science Across Parkinson's (ASAP) Collaborative Research Network, Chevy Chase, MD 20815, USA;
14. CEU, San Pablo University Madrid, E-28938 Mostoles, Spain;
15. Centre Mémoire Ressources Recherches, Service de Neurologie des Maladies Neurodégénératives, Pôle de Neurosciences Cliniques, CHU de Bordeaux, Bordeaux, France ;

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NB.

Abstract should be one page max (all texts and references). No Figure.

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Tauopathies are frequently accompanied by co-pathologies, complicating our understanding of their underlying mechanisms. In this study, we took advantage of a well-established and characterized cohort of baboons previously employed in multiple published investigations[1–4] to examine tau pathology following injection of patient-derived alpha-synuclein aggregates at 6, 12, and 24 months post-injection. Alpha-synuclein aggregates were purified using a sucrose step gradient, and either small or large aggregates were stereotactically injected into the putamen to model progressive neurodegeneration.

Histopathological analyses revealed distinct tau pathology patterns depending on the alpha-synuclein type injected. Baboons injected with small aggregates (n=18) exhibited neuropil threads and neurofibrillary tangles, with no significant differences regardless of post-injection time. Tau pathology spread similarly across rostro-caudal regions, affecting neuronal, oligodendrocyte, and astrocyte cell types, with both 3R and 4R tau isoforms detected in the striatum. In contrast, baboons injected with large aggregates (n=12) displayed neuropil threads but no neurofibrillary tangles. In this group, tau pathology demonstrated differential spreading, with anterior localization in the entorhinal cortex and posterior involvement in the hippocampus, without changes in cell-type specificity or isoform composition.

These results demonstrate the influence of different forms of alpha-synuclein aggregates on tau pathology, providing critical insights into the mechanisms driving tau propagation and lesion formation. This study provides a solid framework for exploring disease mechanisms and developing targeted therapies for tauopathies.

References :

1. Bourdenx M, Nioche A, Dovero S, et al. Identification of distinct pathological signatures induced by patient-derived α-synuclein structures in nonhuman primates. Sci Adv. 2020;6(20):eaaz9165. doi:10.1126/sciadv.aaz9165

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3RD THIRD «PHYSIOPATHOLOGY OF PARKINSON'S DISEASE » (HOPE) MEETING BORDEAUX, JANUARY 29-31, 2025

Morgane Darricau (morgane.darricau@u-bordeaux.fr)

I studied Biology at the University of Bordeaux, where I earned a Master's degree in Nutrition and Food Science. During my internship at the NutriNeuro lab, I investigated the effects of vitamin A deficiency and supplementation on the nigrostriatal system in rat models of Parkinsonism.
I then completed a PhD at the Institute of Neurodegenerative Disease in Dr. Erwan Bezard's team, focusing on tauopathies in non-human primates under the supervision of Dr. Vincent Planche. My research primarily involved immunohistochemistry and biochemistry techniques applied to non-human primate tissues.
Currently, I am a postdoctoral researcher, advancing my work on understanding and modeling these disorders.

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3RD THIRD «PHYSIOPATHOLOGY OF PARKINSON'S DISEASE » (HOPE) MEETING BORDEAUX, JANUARY 29-31, 2025

EPPEC: Understanding Extracellular Diffusion in Multiple System Atrophy Mouse Model

A. Lovisotto,[1] J. Estaùn Panzano,[1*] C. Piva,[2] C. Mazzocco,[1] ML. Arotçarena,[1] Q. Gresil ,[3] I. Calaresu,[4] L. Groc,[4] L. Cognet,[3] E. Bezard .[1]*

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Soria et al. [1] demonstrated that the pathological extracellular space (ECS) in adult mice under degenerative conditions exhibits enlarged dimensions and increased nanoscale diffusion following α-synuclein-induced neurodegeneration. Estaún-Panzano et al. [2] further highlighted that intracellular α-synuclein assemblies, even in the absence of neurodegeneration, can alter ECS rheology and nanoscale diffusion in the striatum.

Expanding on this research, we initiated the ERC PLP PFF ECS study (EPPEC project) to investigate the ECS in pre-formed fibrils (PFF)-injected PLP-synuclein mice, a model of multiple system atrophy, a devastating synucleinopathy where synuclein aggregation mostly occurs in oligodendrocytes. Using PLP-synuclein and Wild Type C57BL6/J mice as controls, animals were injected into the striatum at 2 months of age (AP=+0.5; ML=+2.0; DV=-3.1) with either PFF or PBS, creating four experimental groups: CTR+PBS, CTR+PFF, PLP+PBS, and PLP+PFF. Two time points were planned: 4 months (6 months old) and 10 months (12 months old) post-injection.

Imaging experiments using single-particle tracking (SPT) were performed at each time point. We used two nanoprobes for exploring ECS rheology, namely the Single-walled carbon nanotubes and the Quantum Dots, which can give us insight into the diffusivities and local ECS dimensions, through reconstruction of individual trajectories. Along with the SPT experiments, immunohistochemistry experiments were performed to determine the pSyn signal, enabling the evaluation of protein aggregation under different experimental conditions. Furthermore, transcriptomic analyses will explore gene expression changes associated with ECS alterations and neurodegeneration. These analyses aim to identify specific pathways or molecular signatures implicated in the pathological changes, providing a comprehensive understanding of the underlying mechanisms. By combining these approaches, we aim to uncover novel insights into the relationship between ECS properties and neurodegenerative processes, potentially identifying molecular pathways implicated in disease progression.

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2. Estaún-Panzano et al., Intracellular α-synuclein assemblies are sufficient to alter nanoscale diffusion in the striatal extracellular space. NPJ Parkinsons Dis. 2025

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Anna Lovisotto (*anna.lovisotto@u-bordeuax.fr*). I hold a Master of Science degree in Chemical and Pharmaceutical Technologies, and I am currently pursuing a PhD at the Institut des Maladies Neurodégénératives (IMN) in Bordeaux under the supervision of Dr. Erwan Bezard. My research focuses on the brain's extracellular space, aiming to uncover its role in the misfolding and propagation of toxic proteins associated with Alzheimer's and Parkinson's diseases. Using nanoscopic methods, I investigate the brain's extracellular space, bridging fundamental science with insights into neurodegenerative processes and their underlying mechanisms.

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3RD THIRD «PHYSIOPATHOLOGY OF PARKINSON'S DISEASE » (HOPE) MEETING BORDEAUX, JANUARY 29-31, 2025

Phenotypic characterization of an ATP13A2 knockout rat model of Parkinson's disease

Rémi Kinet [1,], Joanna Sikora[1,2,*], Marie-Laure Arotçarena[1], Melina Decourt[2], Eric Balado[2], Evelyne Doudnikoff[1], Sylvain Bohic[3], Severine Menoret[4], Michele Morari[5], Miquel Vila[6,7,8,9,10], François Georges[1], Erwan Bezard[1], Pierre-Olivier Fernagut[2,†] and Benjamin Dehay[1,†]*

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9. Catalan Institution for Research and Advanced Studies (ICREA), Barcelona, Spain

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Parkinson's disease (PD) is a complex, progressive neurodegenerative affection characterized by the loss of nigrostriatal dopaminergic innervation and the presence of intraneuronal inclusions called Lewy Bodies. Most PD cases are sporadic, but 10- 15% have a familial type. The *ATP13A2* gene encodes a transmembrane lysosomal P5-type ATPase lately linked as a lysosomal polyamine exporter. Mutations in the *ATP13A2* gene were linked as the cause of Kufor-Rakeb syndrome, a juvenile-onset form of PD. Developing an applicable and predictable PD model is still an unmet need for the exploration community to understand better the mechanisms underpinning the pathology and to identify and validate remedial strategies. This study aimed to characterize the first-ever transgenic ATP13A2 knockout rat model to decipher the underpinning mechanisms of ATP13A2-associated pathology. To this end, we performed a comprehensive longitudinal characterization of symptoms and associated neuropathology in this animal model of PD, offering new insights into PD pathogenesis and a potential model for testing and validating healing approaches. To assess whether the omission of the *ATP13A2* gene in rats can replicate human pathology, we followed experimental milestones and longitudinal motor assessment to estimate akinesia and bradykinesia using the stepping test every 3 months up to 12 months of age. Also, we assessed fine motor skills using a reaching task as these deficits are one of the first motor

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symptoms observed in PD cases. The behavioral assessment demonstrated specific experimental poverties in animals with a reduced and completely suppressed ATP13A2 expression. ATP13A2 KO rats displayed age-dependent fine motor deficits and impaired locomotor habituation analogous to those observed in Parkinsonian cases at the early stage of motor symptom onset. We detected significant differences in neuroinflammation in ATP13A2 KO, consistent with the pathology seen in PD brain cases. Moreover, we observed alterations in the autophagy-lysosomal pathway and electrophysiological properties. We also estimated whether a viral-mediated overexpression of α- synuclein or human tyrosinase exacerbates motor and/or cellular deficits in ATP13A2 KO rats. However, we could only observe that overexpression of mutated human alpha-synuclein in substantia nigra showed a difference in the type of α-synuclein-positive aggregates between experimental groups. This ATP13A2 KO rat model could better understand autophagy in PD pathogenesis and open up new therapeutic opportunities to slow the degenerative process in PD patients.

Rémi KINET (*remi.kinet@u-bordeaux.fr*). I'm a 4th year PhD student at the Institute of Neurodegenerative Diseases in the Bordeaux Neurocampus. After a degree in life science specializing in neurosciences at the University of Bordeaux, I entered the Euro-Mediterranean Master in neurosciences and biotechnology. I participated in 3 different internships on the characterization of locomotor and fine-motor skills in PD rat models and the effect of vitamin A deficiency on motor learning. My thesis project focuses on developing a neurodegenerative therapy targeting autophagy restoration and characterizing different PD-animal models.

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3RD THIRD «PHYSIOPATHOLOGY OF PARKINSON'S DISEASE » (HOPE) MEETING BORDEAUX, JANUARY 29-31, 2025

Differential Pathological Dynamics triggered by distinct Parkinson patient-derived α-synuclein extracts in non-human primates

R. KINET[1], M. BOURDENX[1], S. DOVERO[1], M. DARRICAU[1], M.-L. AROTCARENA[1], S. CAMUS[1], G. PORRAS[1], M.-L. THIOLAT[1], I. TRIGO-DAMAS[2,3], S. BOHIC[4], M. MORARI[5], S. CLAVEROL[6], C. TOKARSKI[6], N. KRUSE[7], B. MOLLENHAUER[7,8], C. ESTRADA[9,10], N. GARCIA-CARRILLO[11], M. T. HERRERO[9,10], M. VILA[3,12,13,14,15], J. A. OBESO[2,3,15,16], E. BEZARD[1] AND B. DEHAY[1]

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13 Department of Biochemistry and Molecular Biology, Autonomous University of Barcelona (UAB), Barcelona, Spain;

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Parkinson's disease (PD), Dementia with Lewy Bodies (DLB), and Multiple System Atrophy (MSA), all gathered in the synucleinopathies family disease, share the aggregation of α-synuclein (α-syn) in intracellular inclusions in neurons and/or glial cells as a pathological hallmark. Aggregated forms of α-syn accumulated in neurons are called Lewy Bodies (LB). They are found in PD and DLB and are associated with a dopaminergic neuronal loss in the substantia nigra. We have previously shown that injection of

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patient-derived α-syn aggregates in the striatum of non-human primates (NHP) induces nigral and striatal degeneration of dopaminergic neurons and α-synuclein pathology two years after administration. Here, this study examines the effect of PD-patients derived fraction containing large aggregates (LA) or small aggregated (SA) following striatal injections in baboon monkeys from different ages over time, including various pre-determined time points (6, 12, or 24 months after injection) (n=37). One hundred eighty variables were examined, covering behavioral, histological, and biochemical results. Extensive analysis showed significantly different variables increased between experimental and control groups over time. To understand pathogenic alteration mechanisms, we performed a proteomic analysis of the putamen and the entorhinal cortex, two brain regions strongly impacted at 24 months of this large cohort of NHP. Overall, we observed that experimental groups injected with LA- and SA-enriched fractions followed different neuropathological pathways over time in response to the injection. A significant level of shared variables between LA and SA experimental groups diverged from the control group. Proteomic analysis revealed divergences between LA and SA groups associating mitochondrial deficits in the entorhinal cortex and synaptic alterations in the striatum between both groups.

Rémi KINET (*remi.kinet@u-bordeaux.fr*). I'm a 4th year PhD student at the Institut of Neurodegenerative Diseases in the Bordeaux Neurocampus. After a degree in life science specializing in neurosciences at the University of Bordeaux, I entered the Euro-Mediterranean Master in neurosciences and biotechnology. I participated in 3 different internships on the characterization of locomotor and fine-motor skills in PD rat models and the effect of vitamin A deficiency on motor learning. My thesis project focuses on developing a neurodegenerative therapy targeting autophagy restoration and characterizing different PD-animal models.

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3RD THIRD «PHYSIOPATHOLOGY OF PARKINSON'S DISEASE » (HOPE) MEETING BORDEAUX, JANUARY 29-31, 2025

In vivo targeting α-synuclein fibrils by specific nanobody in mice

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Synucleinopathies (Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy) are a group of neurodegenerative diseases caused by the intracellular accumulation of misfolded α-synuclein. Diagnosing synucleinopathies involves a combination of clinical evaluation, imaging, and pathological examination, with a diagnosis often made late with symptoms well-advanced. While symptom alleviation might be effective (e.g. Parkinson's disease), there is today no cure for combatting the progression of synucleinopathies. Passive vaccination with antibodies is an actively pursued strategy. Among those, an emerging strategy involves nanobodies targeting α-synuclein aggregates. Nanobodies are smaller and more stable than conventional antibodies, allowing them to penetrate the blood-brain barrier efficiently. They could be engineered to bind α-synuclein aggregates to promote their specific clearing for diagnostic and therapeutic purposes.

This pilot feasibility study aims at *in vivo* imaging α-synuclein-specific recombinant nanobodies raised against various single or multiple epitopes in an α-synuclein pre-formed fibril (PFF) mouse model. Using fluorescence reflectance imaging (FRI) and molecular tomography (FMT), we longitudinally follow, in the same mice, for 4 months on the one hand, the intracerebrally delivered PFF, and on the other hand, the intraperitoneally administered nanobodies. B6 *albinos* male mice were injected with PFF labeled with IVISense 800 nm dye in the striatum. Two or four months after the model induction, the mice received an intraperitoneal injection of nanobodies against α-synuclein fibrils labeled with IVISEnse 680 nm dye. Following in vivo imaging, 72 hours after the nanobodies injection, *ex vivo* imaging and immunofluorescence on brain slices were carried out.

We show the *in vivo* follow-up of the PFF over time. After intraperitoneal injection, nanobodies biodistribution revealed intense staining in the kidney (elimination) and a hot spot in the brain that matches with the PFF delivery. The *ex vivo* imaging confirms the co-localization. Immunofluorescence against P(Ser129)-α-synuclein plus direct detection of the nanobodies by confocal imaging revealed an accumulation of the nanobodies in the striatum in the area of the PFF injection (but not on contralateral hemisphere), with also detection of both P(Ser129)-α-synuclein and nanobodies in the *substantia nigra* following the spread of misfolded α-synuclein.

Here, we pioneer the *in vivo* targeting and monitoring of α-synuclein fibrils by specific nanobodies using optical imaging. The data suggest that these nanobodies could be used therapeutically to combat synucleinopathies.

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Dopaminergic physiology in the substantia nigra pars compacta of recombinant a-synuclein pre-formed fibrils injected mice

Jakob Scharnholz,[1] Claire Mazzocco[1], Marie-Laure Arotcarena [1], Erwan Bezard[1], Jérôme Baufreton[1]
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Parkinson's Disease (PD) is a neurodegenerative disorder manifesting motor and non-motor symptoms. From a pathological point of view, it is characterised by the presence of intracellular inclusions called Lewy Bodies (LB) and neuronal loss, primarily, but not exclusively, of the dopaminergic neurons in the substantia nigra pars compacta (snDAN). Importantly, disease progression is long and believed to be concurrent with different pathological stages and neurological symptoms[1]. However, a description of physiological alterations of snDANs at various disease stages is lacking mainly due to the limitation of fast onset and late-stage restricted animal models such as 6-OHDA. Recently, the development of new animal models enabled the investigation of the progressive nature of PD-associated pathology. Still, few studies have assessed electrophysiological aspects in those models.

Here, using a mouse model of endogenous aggregation without concomitant neurodegeneration, we isolated the inclusion-relevant feature of PD-associated pathology, distinguishing it from neuronal loss. Therefore, unilateral striatal injection of recombinant α-synuclein pre-formed fibrils (PFFs) was performed. Since alterations of snDAN physiology and Parkinsonian motor symptoms are associated[1], we compared ex vivo patch clamp recordings between PFF and control-injected mice. It had been recently suggested that cortical physiology showed a difference between aggregate+ and aggregate- neurons from PFF-injected mice[2]. Due to a small number of recorded neurons, we determined the distance of recorded neurons and their closest aggregate. Overall, we did not observe any alterations of passive properties such as spontaneous firing rate, membrane potential, and voltage sag. However, we observed a reduction in firing rate upon injection of large positive currents.

Animal models of early Parkinson-associated pathologies, such as the PFF modality, do not show overt motor symptoms. The mostly unchanged physiology of snDAN was therefore not surprising. Finally, the finding of a reduced evoked firing rate reminiscent of phasic dopaminergic firing offers an interesting direction for further investigations.

1 L. V. Kalia and A. E. Lang. Parkinson's disease. The Lancet, 386:896–912, 8 2015. ISSN 01406736.
2 L. Chen, H. D. Chehade, and H.-Y. Chu. Motor cortical neuronal hyperexcitability associated with -synuclein aggregation. bioRxiv, 2024

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2023 -	PhD student University of Bordeaux, France supervised by Jérôme Baufreton
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Exploring Motor and Non-Motor Symptom Progression in a Synucleinopathy Mouse Model of Parkinson's Disease

Emma PERROT[1], Christelle GLANGETAS[1], Adriane GUILLAUMIN[1], Elodie LADEVEZE[1], Erwan BEZARD[1], Jérôme BAUFRETON[1], François GEORGES[1]

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Parkinson's disease (PD) is a neurodegenerative disorder affecting millions worldwide and is the second most common neurodegenerative disease. It is marked by early non-motor symptoms, followed by characteristic motor symptoms. Diagnosis relies on motor signs resulting from significant dopaminergic neuron loss in the substantia nigra pars compacta. Evidence suggests that neurodegeneration begins years before motor symptoms, with early non-motor symptoms involving emotional brain structures. PD is thus a multidimensional disease, associated with a number of non-motor symptoms including anxiety that can contribute to a significantly impact patient's quality of life.

Risk evaluation, vigilance and anxiety are physiological adaptive responses that helps the body prepare for potentially dangerous situations. These responses can become maladaptive, creating a feedback loop where anxious individuals overestimate risks. This heightened perception creates a state of hypervigilance, which then amplifies anxiety.

However, the neurobiological basis of PD-related anxiety remains poorly understood. The dorsal raphe nucleus (DRN) contains unique dopamine neurons (DRNDA) projecting to the Central Amygdala (CeA) and bed nucleus of the stria terminalis (BNST), critical regions implicated in anxiety. We hypothesize that the functional decline of DRNDA neurons contributes to anxiety development in PD.

To investigate this hypothesis, we used the SNCA-ovx murine model of PD[1], which overexpresses a mutated human alpha-synuclein protein known to form aggregates over time. This progressive and non-invasive model is particularly relevant to our study as it allows us to identify the early emergence of non-motor symptoms, which are often absent in other models that focus on severe motor symptoms.

We assessed risk-assessment behavior, anxiety levels, and motor function using a behavioral protocol combining various tests related to anxiety and vigilance, conducted on male and female mice at 6, 12, and 18 months. Initial results at 6 and 12 months reveal transient anxiety symptoms at 6 months, which resolve by 12 months, giving way to emerging motor deficits. This study is ongoing (18 months) and will require further experiments to challenge our circuit-based hypothesis.

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3RD THIRD «PHYSIOPATHOLOGY OF PARKINSON'S DISEASE » (HOPE) MEETING BORDEAUX, JANUARY 29-31, 2025

Emma PERROT

PhD student in Neurosciences – 1st year
Research director: François GEORGES

I'm working on the development of early anxiety in Parkinson's disease to understand the circuits and neuronal populations underlying its regulation.

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DEGREE

2021-2023 - **International Master in Neurosciences**, University of Bordeaux, Neurocampus (France)
2018-2021 - **Bachelor in Life Sciences**, Cellular biology and physiology, UFR Sciences and techniques (Limoges campus, France).

EXPERIENCE

Internship

2023 - UMR5293 CNRS, Jérôme BAUFRETON (6 months)
Team Dopamine & Neuronal assemblies - Broca center, Bordeaux (France)
Subject: Functional characterization of arkypallido-striatal pathways in physiological condition in mice
Experiments: patch clamp, electrophysiology, optogenetic, extraction of mouse brain, imaging, immunohistochemistry, acute slices

2022 - UMR5293 CNRS, FOSSAT Pascal (2 months)
Team Monoamines, Parkinson and Pain - Broca center, Bordeaux (France)
Subject: Involvement of spinal inhibitory interneurons in serotonergic descending control of pain
Experiments: Immunohistochemistry, imaging (epifluorescence, confocal), viral injection, optogenetic.

Scientific mediation

2022-2024 - President of Neurosciences of Bordeaux Association (NBA) – Different events related to Neuroscience
2023 and 2024 - Brain Week in Bordeaux: Science popularization and awareness of Brain Research
2024 - "Le marché des connaissances" - Awareness Workshop on brain research
2024 - Scientific circuit in Bordeaux – Scientific Workshop for High School students, exploring the research profession through immersion in ongoing projects

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Harnessing chaperone-mediated autophagy through viral- based LAMP2A overexpression in the Lewy body-injection non-human primate model of Parkinson's Disease

M.-L. AROTCARENA[1], M. FOUKA [2], M. GIANNOPOULOU [2], A. LOVISOTTO [1], H. JADOT [1], M. DARRICAU [1], E. BALPE[1], M. ACHOUR [1], L. STEFANIS [2], E. BEZARD [1], M. XILOURI [2], B. DEHAY [1]

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Lysosomal impairment is strongly implicated in Parkinson's disease (PD). Chaperone-Mediated Autophagy (CMA) is a major lysosomal pathway responsible for alpha-synuclein (aSyn) clearance but, at the same time, can be a direct target of aSyn-related neurotoxic effects. The rate of CMA depends mainly on the levels of LAMP2A (lysosomal transmembrane protein 2A) and the presence within the lysosomal lumen of the lys-HSC70 chaperone. This project aimed to investigate whether the CMA lysosomal pathway induction may improve the pathology induced by patient-derived Lewy body (LB) brain injections in non-human primates, by targeting CMA's rate-limiting step, the LAMP2A receptor. To this end, we performed bilateral injections of the AAV2/9-LAMP2A-HA vector (or the control Stuffer vector) in the SNpc of 14 male rhesus macaque monkeys (Macaca mulatta) together with unilateral intrastriatal injections of low doses of aSyn-containing LB extracts purified from the SNpc of PD brains (or extracts from non-PD brains as control). 15 months later, extensive histochemical and biochemical analyses were performed. We characterised the pattern of dopaminergic loss in the striatum and the substantia nigra, the regional distribution of aSyn immunoreactivity in several brain structures, as well as its pathological status (i.e., S129 phosphorylation) and the occurrence of lysosomal dysfunction. Overall, our data so far show that viral-mediated LAMP2A overexpression protects dopaminergic neurons from the cell loss induced by the injection of PD brain extracts. Interestingly, LAMP2A-injected animals displayed significantly improved performance in the behavioral tests related to pre-frontal cortex-dependent cognitive function, suggesting that our gene therapy approach induces a beneficial cognitive effect. Lastly, LAMP2A overexpression decreases extracellular aSyn levels in the monkey biological fluids. In conclusion, this study demonstrates that viral-based overexpression of LAMP2A attenuates the dopaminergic neurodegeneration in a non-human primate model of PD. These results support the idea that enhancement of CMA through LAMP2A overexpression or other means, possibly pharmacological, might open new therapeutic opportunities for slowing down the degenerative process in patients with PD and related synucleinopathies.

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2019-2020 Post-doctoral fellowship (France Parkinson Association)
Team Physiopathology of Proteinopathies, IMN (Institute of Neurodegenerative Diseases, CNRSUMR 5293, Bordeaux, France).

2016-2020 PhD in Neurosciences, University of Bordeaux
Team Physiopathology of Proteinopathies, IMN (Institute of Neurodegenerative Diseases, CNRSUMR 5293, Bordeaux, France). Supervised by Dr. Benjamin Dehay.

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3RD THIRD «PHYSIOPATHOLOGY OF PARKINSON'S DISEASE » (HOPE) MEETING BORDEAUX, JANUARY 29-31, 2025

Human TFEB overexpression prevents mutant human A53T–α-synuclein toxicity in a prevention design applied to a rat model of Parkinson's disease

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Parkinson's disease (PD), a synucleinopathy characterized by neurodegeneration and neuronal α-synuclein intracytoplasmic inclusions named Lewy Bodies, is associated with impairment of the autophagy-lysosomal pathways (ALP). Increased expression of the master regulator of ALP, transcription factor EB (TFEB), is hypothesised to promote the clearance of WT α-synuclein and survival of dopaminergic neurons.

Here, we explored the efficacy of targeted human TFEB overexpression in nigral neurons to reduce the pathological burden of α-synuclein in a viral-based rat model of nigral human A53T α-synuclein overexpression. To assess whether the timing of therapeutic intervention application vis-à-vis the pathological trigger matters, we evaluated the effects of AAV-hTFEB in three experimental designs: (i) in a therapeutic setting (i.e., striatal AAV-hTFEB injection at one-month p.i. after nigral AAV-Synuclein injection) and two prevention settings (ii) concomitant injections of nigral AAV-hTFEB and AAV-Synuclein; and (iii) concomitant injections of nigral AAV-Synuclein and intrastriatal AAV-hTFEB. All groups were behaviourally followed. The brains were harvested four months after AAV-Synuclein injection. Extensive histochemical analyses were performed to evaluate cerebral pathological markers known to be affected in PD. We characterised the human TFEB expression, the pattern of dopaminergic loss in the striatum and the substantia nigra, the regional distribution of α-synuclein immunoreactivity in several brain structures, as well as its pathological status (i.e., S129 phosphorylation). We observed that human TFEB was correctly expressed in the rat substantia nigra and the striatum. Human TFEB nigral expression was sufficient to prevent nigrostriatal neurodegeneration in this PD rat model both at the cell body (substantia nigra) and terminal (striatum) levels when injected only at the nigra level. This beneficial effect was associated with a decreased accumulation of α-synuclein into the substantia nigra and a strong clearance of phosphorylated (S129) α-synuclein.

Our study confirms the disease-modifying potential of human TFEB by extending the demonstration to an AAV-A53T synuclein rat model and, for the first time, validating the human version of TFEB transgene, paving the way for gene therapy of PD.

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3RD THIRD «PHYSIOPATHOLOGY OF PARKINSON'S DISEASE » (HOPE) MEETING BORDEAUX, JANUARY 29-31, 2025

Dissecting the role of LRRK2 in intercellular communication using iPSC-derived neuron-glia tricultures

Carmela Giachino [1,2], Federico Bertoli [1,2], María José Pérez J [1,2,3], Romane Lasmarrigues [1,2], and Michela Deleidi[1,2,3]

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The complex and dynamic interplay between glial cells and dopaminergic neurons (DAns) in the pathogenesis of Parkinson's disease (PD) remains elusive to date. Over the past two decades, compelling evidence has highlighted leucine-rich repeat kinase 2 (LRRK2), a kinase linked to both autosomal inherited and sporadic Parkinson's disease (PD), as a critical regulator of cell-cell communication (1,2). Furthermore, the implication of LRRK2 in immune-related disorders, its high expression in immune cells, and its role in pathways relevant to immune cell function, have established this kinase as a key modulator of inflammatory responses (3,4,5,6). Here, we hypothesized that LRRK2-G2019S, the most common PD-associated variant, might affect neuron-glia communication under basal and inflammatory conditions. To test this hypothesis in a disease-relevant model, we developed an iPSC-derived triculture system comprising neurons, astrocytes, and microglia, and analyzed cell-type-specific signatures using single-cell RNA sequencing. In addition, to determine if and how the LRRK2-G2019S variant affects intercellular communication under inflammatory conditions, LPS-treated tricultures were examined and compared to basal conditions. We found that LRRK2-G2019S significantly affects the transcriptional signatures of these three cell types. In microglia, both chemotactic ability and inflammatory responses are affected, even under basal conditions. In neurons and astrocytes, genes involved in synaptic plasticity, neuronal survival, and cell-cell interactions are dysregulated. LPS stimulation exacerbates these effects, with calcium signalling pathways in microglia being particularly impaired. To gain deeper insights into how intercellular communication may be impaired in our model, we are leveraging CellChat analysis. Elucidating key molecular perturbations in the glia-neuron dialogue will help to elucidate the underlying mechanisms of neurodegenerative diseases and potentially guide the development of targeted therapeutic interventions.

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Giachino Carmela (*carmela.giachino@institutimagine.org*)

My studies allowed me to achieve a multifaceted education ranging from cellular biology to bioorganic chemistry and ultimately neuroscience. During my PhD program I investigated how the aging process together with inflammation contribute to onset of PD LRRK2-mediated. I have been part of a Coen grant as fellow, which gave me the opportunity to get insight into the neurodegenerative diseases field.

27/02/2023-current	**Post-doctoral fellow at Imagine Institute, Paris, France**
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27/07/2018	Master's degree in Biomolecular chemistry
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3RD THIRD «PHYSIOPATHOLOGY OF PARKINSON'S DISEASE » (HOPE) MEETING BORDEAUX, JANUARY 29-31, 2025

Title: Investigating early mechanisms of alpha-synuclein pathology in iPSC-derived midbrain organoids

Authors/affiliations: Federico Bertoli[1,3], Hariam Raji[1,3], Alicia Lam[1], Laura Volpicelli-Daley[3,4], Michela Deleidi[1,2,3]

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During the early stages of Parkinson's disease (PD), the misfolding and aggregation of alpha-synuclein (α-syn) are observed in the patient's brain. While these events are associated with changes in cellular homeostasis and metabolism, the causal link to the selective degeneration of dopaminergic neurons in later stages remains poorly understood. This lack of knowledge is largely due to the limitations of current PD models that fail to recapitulate the intricate events associated with α-syn pathology in the human brain. Here, we developed induced pluripotent stem cell (iPSC)-derived midbrain organoids as a more advanced and accurate model to investigate the dynamics and mechanisms underlying early events in α-syn pathology in PD. We induced endogenous α-syn aggregation in midbrain organoids by treating them with α-syn preformed fibrils (PFFs) and analyzed the early response five days after PFF treatment by immunostainings and single-cell transcriptomics. Midbrain organoids treated with α-syn PFFs showed neuronal uptake of α-syn fibrils, colocalization of PFFs with lysosomes, and the presence of p-Ser129 α-syn.

Single-cell RNA sequencing revealed PFF-associated changes in a distinct dopaminergic neuron subpopulation characterized by the expression of PD vulnerability markers (TH, SOX6, KCNJ6, SNCA). Differential gene expression analysis between dopaminergic neurons susceptible to PFF treatment and controls showed a downregulation of oxidative phosphorylation pathways, and an upregulation of protein degradation pathways, suggesting impaired energy metabolism and an active response to counteract proteotoxic stress. Notably, we observed a selective downregulation of the mitochondrial enzyme nicotinamide mononucleotide adenylyltransferase 3 (NMNAT3) in dopaminergic neurons affected by PFF treatment. This finding suggests an alteration in mitochondrial NAD^+ metabolism, potentially exacerbating mitochondrial dysfunction and contributing to the heightened susceptibility of these neurons to α-synuclein pathology.

In our study, we demonstrate that iPSC-derived midbrain organoids serve as a valuable model for investigating the early stages of α-syn pathology. Additionally, we provide new insights into the mechanisms underlying DA neuron vulnerability in PD.

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Part of the NADIS consortium (https://www.nadis.eu/)

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3RD THIRD «PHYSIOPATHOLOGY OF PARKINSON'S DISEASE » (HOPE) MEETING BORDEAUX, JANUARY 29-31, 2025

Monitoring α-synuclein seeding and discrimination of amyloids amplified in vitro from biological samples

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Synucleinopathies, such as Parkinson's disease, Dementia with Lewy bodies, and Multiple system atrophy, are neurodegenerative diseases characterized by the accumulation of alpha-synuclein (α-syn) amyloid fibrils in neurons or glial cells. α-syn is an intrinsically disordered protein and can undergo conformational changes, leading to its aggregation. Synucleinopathies have distinct phenotypes: the symptoms, the affected brain regions and the cell types showing α-syn are different. A growing body of evidence show that these differences are associated with different structures of amyloid fibrils (polymorphism).
Diagnosis of synucleinopathies is based on clinical assessment of the patient, as there is no biological test available. In the last few years, seed amplification assays (SAA) have been developed to assess seeding properties of the different brain-extracted fibrils, and to be used for diagnosis. SAAs are based on the capacity of α-syn amyloids to seed the aggregation of recombinant monomeric α-syn. Usually, the amplification process is monitored with a fluorescent amyloid probe, ThT[1]. However, several groups reported that ThT does not bind equally α-syn fibril polymorphs[1,2]. Furthermore, ThT could act as a scaffold and guide the structure of newly-formed fibrils. Thus, we need to find a fast structure-independent method to monitor aggregation.
As described previously, widely used technics to study α-syn amyloids, such as western-blot, do not allow a precise quantitation of α-syn amyloids in the samples[3]. Therefore, we aim to develop a ThT-free SAA to detect and amplify α-syn fibrils from biological samples, such as cerebrospinal fluids and brain homogenates, by using an in-house ELISA specifically detecting the different α-syn species. We are also planning to use a new method, the fibrilloscope, as an end-point measure, to discriminate the amplified fibrils[2].

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Ludivine Sabatier (*ludivine.sabatier@u-bordeaux.fr*)

I did my bachelor in biochemistry in La Rochelle and my master in biochemistry and biomolecular biology in Rennes. I am now a PhD student at the Institute of Neurodegenerative Diseases in Bordeaux, in the team "Integrative neuropathology of α-synucleinopathies" led by François Ichas and Francesca De Giorgi-Ichas. Under the supervision of Florent Laferrière, I am working on the characterization of alpha-synuclein amyloids derived from biological samples of patients with synucleinopathies.

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3RD THIRD «PHYSIOPATHOLOGY OF PARKINSON'S DISEASE » (HOPE) MEETING BORDEAUX, JANUARY 29-31, 2025

Antiepileptic Drugs and Parkinson's Disease: A Meta-Analysis of Existing Evidence

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ABSTRACT

Purpose: There is growing interest in the association between antiepileptic drugs (AEDs) exposure and subsequent Parkinson's disease (PD). Recognizing this, the aim of this study is to conduct a meta-analysis to provide a critical summary of the association between AEDs and PD.

Methods: We conducted a literature search of PubMed, SCOPUS, and Web of Science databases up to October 2024. We identified studies using an observational design, and performed a meta-analysis to evaluate the association between AEDs exposure and incident PD. We assessed the quality of the studies and identified the pooled odds ratio (OR) for those exposed to AEDs compared with those who were not. Heterogeneity was investigated using the I^2 statistic and significance was determined using Cochran's Q-test. An additional Bayesian analysis was used to test the accuracy of the estimations, and a post-hoc Egger's regression test was performed to evaluate the small study bias. This study was registered in PROSPERO.

Results: Of the 1775 unique studies identified, 55 were selected for full-text review. Five studies (N = 127,324) were eligible for inclusion. Quality assessment revealed moderate-to-high methodological quality in the included studies. The overall OR for incident PD was 1.82 times (95% CI: 1.35-2.45) higher for AEDs recipients. When considering each drug individually, the association was highest for valproate (OR 3.94 (95% CI: 3.15-4.92) and lowest for carbamazepine (OR 1.32 (95% CI: 1.16-1.49). Further, Bayesian analysis revealed overlapping estimates.

Conclusion: Despite the significant associations observed, the existing evidence is still insufficient, making it premature to draw inferences about the association between AEDs and PD. Further well-designed studies are required to explore this relationship. Any observed associations should be interpreted with caution.

Ruslan Akhmedullin (*ruslan.akhmedullin@nu.edu.kz*). Ruslan Akhmedullin is a researcher at the Department of Medicine, Nazarbayev University School of Medicine, Astana, Kazakhstan. His work focuses on neurodegenerative diseases epidemiology and evidence synthesis methods.

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3RD THIRD «PHYSIOPATHOLOGY OF PARKINSON'S DISEASE » (HOPE) MEETING BORDEAUX, JANUARY 29-31, 2025

A combination of antidiabetics achieves neuroprotection in a cellular model of Parkinson's disease

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Parkinson's disease affects 10 million patients worldwide. It represents a considerable socio-economic burden, a burden spreading among the population, including across an increasing number of people under 50 years. Currently, available authorized treatments only hide the major symptoms for a few decades, their efficacy wearing off with disease progression. **There is an unmet need for a neuroprotective, disease-modifying treatment.**

We present and develop a **combination of antidiabetic drugs**, namely metformin and glibenclamide, with a synergistic, neuroprotective effect *in vitro*. In a rat primary mesencephalic neuron model of Parkinson's disease using 6-OHDA as toxic agent**, we show a significant effect on both neurone viability and fitness, superior to that of ambroxol** (currently developed as a promising neuroprotective agent in Parkinson's disease).

Our treatment combines glibenclamide and low-dose metformin, in a patented formulation. The **concomitant administration** of specific dose ranges of these two drugs **restores cell viability and survival in an induced model of diseased neurons**. The mechanisms explaining the synergy between the two molecules are currently being studied, involving orthogonal mechanisms related to both NLRP-3-dependent inflammation and oxidative stress in dopaminergic neurons, mitochondrial stress, and tightening of the blood-brain barrier.

Based on these results, **we are currently conducting preclinical studies aimed at characterizing the neuropharmacokinetics of the molecules, carrying out an effective dose search**, and characterizing their neuroprotective effect on *in vivo* murine models. These experiments will serve as a basis for the regulatory dossier for the first clinical trial planned for the beginning of 2026.

Guillaume Brachet (*Guillaume.brachet@cxstherapeutics.com*).

Guillaume Brachet is a Pharm.D. Ph.D. from Tours. He is the co-founder and CEO of CXS Therapeutics, a medtech involved in the identification and redevelopment of drugs for the treatment of neurological diseases. In 2022, four years after receiving a diagnosis of Young Onset Parkinson's Disease, he decided to initiate this project, soon joined by a full team of six scientists and experts in bioinformatics, drug development and licensing. In 2023 and 2024, CXS Therapeutics successfully achieved two series of fundraising, allowing to bear the regulatory preclinical development of its drug candidates, and the building of a proprietary methodology for the identification of relevant candidate molecules ready to be studied for their potential in the treatment of various neurological diseases.

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3RD THIRD «PHYSIOPATHOLOGY OF PARKINSON'S DISEASE » (HOPE) MEETING BORDEAUX, JANUARY 29-31, 2025

Use of long-read whole genome sequencing to solve exome negative early-onset and familial Parkinson's disease cases

Guillaume Cogan [1,2,3], Kensuke Daida [1,2], PhD1,2, Kimberley J. Billingsley[1,2], Christelle Tesson[3], Sylvie Forlani[3], Ludmila Jornea[3], Andrew B. Singleton[1,2], Hélène Gervais Bernard[4], Suzanne Lesage[3], Cornelis Blauwendraat[1,2], Alexis Brice[3]

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Objectives: To solve undiagnosed Parkinson's disease (PD) patients who underwent multiple genetic testing and identify new PD genes.

Methods: Samples from 106 individuals from the Paris Brain Institute were selected for long-read whole genome sequencing (LRS). They were all left undiagnosed for known PD genes after whole exome sequencing. Ninety seven individuals belonged to 40 families whereas nine were early-onset (< 25 years old) isolated cases. The average age at onset was 46.8 years old (range 10 to 79 years). LRS was performed at the Center for Alzheimer's disease and Related Dementias at the National Institutes of Health from february to august 2023 according to the standard protocol.

Results: Preliminary analysis identified two interesting results. Firstly, a compound heterozygous deletion encompassing exon 3 and 4 and duplication encompassing exon 3 was identified in *PRKN* gene in two siblings showing a typical *PRKN*-PD phenotype. Multiple prior genetic tests were not able to reveal this complex rearrangement.

Secondly, LRS revelaed a heterozygous frameshift deletion of exon 3 in *PDE10A* in four patients from a family including seven affected members. *PDE10A* is sensitive to haplo-insuffisance (LOEUF score = 0.43) and is exclusively expressed in the basal ganglia. Mono and biallelic pathogenic variants in *PDE10A* cause a non-progressive childhood onset hyperkinetic movement disorder. Interestingly, one patient who reached the age of 60 developed Parkinson's disease in the literature. Segregation analysis of the deletion suggests an incomplete penetrance and a variable expression, including lewy body dementia and essential tremor. Analysis of GP2 and AMP-PD cohorts showed 67 additional PD patients with rare missense variants and three with truncating mutations. Whether these cases are familial or not is under investigation.

Conclusions: LRS appears as an efficient tool to decipher the genetic architecture of unsolved complex neurological disorders such as PD.

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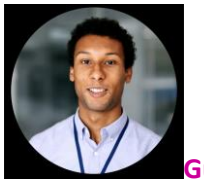

Guillaume Cogan (*Guillaume.cogan@icm-institute.org*). I have an MD in Medical Genetics, a Master of Science and a Master of Arts in Science Ethics. I am currently a PhD student at the Paris Brain Institute, working in the genetic landscape of neurodegenerative disorders, more specifically Parkinson's disease. I use whole exome sequencing and whole genome long-read sequencing data to find new genes involved in Parkinson's Disease.

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RFC1 EXPANSIONS : A RARE CAUSE OF PARKINSONISM

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3. Sorbonne Université, Paris Brain Institute, APHP, INSERM, CNRS, F-75013 Paris, France

Introduction. Cerebellar ataxia with neuropathy and vestibular areflexia syndrome (CANVAS) is a neurodegenerative disease caused by biallelic mutations in the *RFC1* gene, mostly $(AAGGG)_n$ expansions in intron 2 [1]. Several studies reported null variants in patients [2,3] supporting the hypothesis of a loss-of-function mechanism. Our team revealed that 10% of CANVAS patients had parkinsonism, a rate 10-fold higher than matched population of similar age [4]. Moreover, rare cases of *RFC1* biallelic expansions have been reported in patients with atypical parkinsonism. Our hypothesis is that parkinsonism is an entryway into *RFC1* pathology.

Methods. We screened for *RFC1* pathogenic expansions in four cohorts of patients with Parkinson's disease (PD) (n=744), inherited parkinsonism (n=846), atypical PD with dysautonomia (n=368) and multiple system atrophy (MSA) (n=194). We used the methods of molecular diagnosis of CANVAS, with a duplex fluorescent PCR, three repeat-primed PCR and a long-range PCR with southern blot revelation.

Results. We uncovered 10/2151 (0.46%) biallelic $(AAGGG)_n$ *RFC1* expansions in our four cohorts with a higher frequency of homozygous carrier in MSA cohort (3/194 ; 1,55%). These patients' phenotypes consist in three atypical PD with dysautonomia, one atypical PD with cerebellar syndrome, one typical *RFC1*-related disorders and three probable MSA without sensory neuropathy. Two patients had a classical PD for 6,5 years and were treated by neurostimulation.

Conclusions. Our results favor an association between *RFC1* mutations and parkinsonism. Further phenotypic characterizations are needed to propose guidelines for the molecular screening, but some patients have a phenotype undistinguishable from a classical PD. We suggest that patients with unknown causes of inherited parkinsonism or MSA be screened for *RFC1* mutations.

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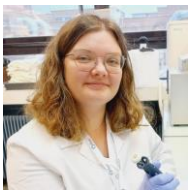

Violette Delforge (*violette.delforge@inserm.fr*). I am a PhD student in neurosciences, currently in my second year. I am working on the link between repeat expansions in the *RFC1* gene and parkinsonism, under the supervision of Dr. Vincent Huin. Together we published a review "*RFC1: Motifs and phenotypes*" available on https://doi.org/10.1016/j.neurol.2024.03.006 .

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3RD THIRD «PHYSIOPATHOLOGY OF PARKINSON'S DISEASE » (HOPE) MEETING BORDEAUX, JANUARY 29-31, 2025

The Pyruvate Dehydrogenase as a new potential therapeutic target in Parkinson's disease pathophysiology

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Parkinson's Disease (PD) is a progressive and incurable neurodegenerative disease characterized by an irreversible loss of nigrostriatal dopaminergic neurons[1]. Its symptomatology evolves over the years from a prodromal stage, including neuropsychiatric symptoms such as loss of motivation and anxiety, to a clinical stage with significant motor impairments[2]. Today, the causes of PD pathogenesis are still poorly understood.

In this context, we recently performed a large translational metabolomics study on serum and brain samples of both rat and non-human primate PD models and newly diagnosed PD patients, which revealed a decoupling between the glycolysis and the Krebs cycle[3]. These metabolic perturbations strongly suggest that impairments of the Pyruvate Dehydrogenase (PDH), the key enzyme linking these two metabolic pathways, could be a major actor in the mechanisms underlying the pathogenesis of PD. Consistently, it have been shown that the congenital mutation of the PDH can leads to the development of a Leigh syndrome with neurodegeneration of the nigrostriatal pathway[4] and that the PDH is downregulated in the nigrostriatal pathways of patients with idiopathic PD[5].

Based on this, our work aims to better decipher the role of this enzyme in PD pathophysiology by inducing a local PDH downregulation in the nigrostriatal pathway of healthy rats by using a AAV-microRNA strategy and stereotaxic surgery. The results show that this strategy has induced a 40% nigrostriatal PDH downregulation, resulting in the development of a hypo-motivated state with anxious behaviors but without motor impairments. These symptoms are reminiscent of a prodromal-like PD symptomatology[5], and they are associated with the evidences of a parkinsonian-like metabolic profile in both blood and brain. In addition, whereas no sign of dopaminergic neurodegeneration were observed by immunostaining, a significant depletion of the striatal level of tyrosine hydroxylase was highlighted by western blot. Altogether, these results indicate that a PDH dysfunction could be involved in PD pathophysiology since the early stage and that, consequently, PDH could be considered as a new potential therapeutic target.

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Vanille Millasseau (*vanille.millasseau@univ-grenoble-alpes.fr*).

Currently a PhD student at Grenoble, my work focuses on Parkinson's disease, with two lines of research: a clinical project aimed at developing a blood biomarker for the early diagnosis of PD, and a preclinical project evaluating PDH as a potential therapeutic target. I did my bachelor's and master's degree in neurosciences in Grenoble and remained there to do my thesis in the same laboratory as my M2 internship, so that I could continue doing the research that drives me and enjoy the mountain setting.

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3RD THIRD «PHYSIOPATHOLOGY OF PARKINSON'S DISEASE » (HOPE) MEETING BORDEAUX, JANUARY 29-31, 2025

Assessing Modulation of LRRK2:14-3-3 interaction on Parkinson's Disease-associated cellular phenotypes

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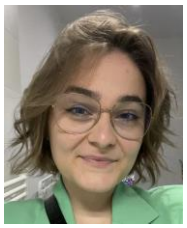
The Leucine-Rich Repeat Kinase 2 (LRRK2) is a large multi-domain protein with a functional GTPase and kinase domain. The gene is mutated in familial and idiopathic Parkinson's Disease (PD) cases and mutations enhances kinase activity and also abnormalities in lysosomal function. To date, studies of LRRK2 kinase inhibition in preclinical models have highlighted side effects in peripheral tissues (lung, kidney). LRRK2 protein forms a complex with 14-3-3 proteins that requires the phosphorylation of heterologous Ser910 and Ser935 sites within LRRK2. Autophosphorylation of these sites is decreased in PD-associated mutants and increased upon 14-3-3 overexpression. The dephosphorylation leads to a closed conformation of LRRK2 and alterations in subcellular localization, while the cytoplasmic localization of LRRK2 is maintained when LRRK2:14-3-3 interaction is preserved, suggesting that preserving the LRRK2:14-3-3 complex may be beneficial against PD. The aim of the study is to assess how the modulation of the complex affects molecular and cellular phenotypes of LRRK2. In this work, we used pharmacological compounds and phosphorylation site mutants of LRRK2 that can disrupt and/or prevent the interaction of LRRK2 and 14-3-3. The *in cellulo* interaction of phosphorylation mutants LRRK2 and 14-3-3 has been tested by co-immunoprecipitation and the LRRK2 recruitment to lysosomes has been studied by immunocytochemistry in HEK293T cells during a lysosomal membrane permeabilization induced by chloroquine. At the same time, we evaluated the sensitivity of LRRK2 to MLi-2, a well-known LRRK2 kinase inhibitor, in conditions of 14-3-3 overexpression or inhibition. Finally, we tested for the first time, the effect of patented compounds, molecular glues that can stabilize LRRK2:14-3-3 interaction, on LRRK2 phosphorylation status at Ser935 site and the ability to counteract MLi-2 effect. Our preliminary results show changes in lysosomal recruitment of LRRK2 phosphomutants compared to LRRK2 WT, and a positive effect of LRRK2:14-3-3 molecular glues on LRRK2 phosphorylation. These experiments deepen our knowledge on the modulation and importance of the LRRK2:14-3-3 complex, an interesting target for PD treatment.

Margaux Morez (*margaux.morez@inserm.fr*).



Post-doctoral researcher (*2nd year*)

My PhD project (defence in 2023) was in the field of neuropathic pain. I worked mainly on mouse models of chemotherapy-induced neuropathy. I assessed the *in vivo* effect (behavioural task) of *peptoid* that disrupt protein-protein interaction. Now I'm on a post-doc project in the field of Parkinson's disease, and especially on LRRK2 protein (MJFF project). The aim is to study the *in cellulo* activity of small molecules that can stabilize LRRK2:14-3-3 interaction

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3RD THIRD «PHYSIOPATHOLOGY OF PARKINSON'S DISEASE» (HOPE) MEETING BORDEAUX, JANUARY 29-31, 2025

Nanovectors for lysosome-based therapeutic strategies against neurodegenerative diseases

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Parkinson's disease (PD) and other neurodegenerative disorders stand as a critical health and social concern with these complex and age-related diseases, which are characterized by a selective neuronal vulnerability, including degeneration in specific brain regions like the substantia nigra hosting dopaminergic neurons and deposits of misfolded proteins in PD. It has been hypothesized that dysfunction in the autophagy-lysosomal pathway (ALP) clearance mechanism contributes to the growth of pathogenic elements in neurodegenerative conditions. Lysosomes play a central role in clearing out persistent proteins like α-synuclein and eliminating tired-out or impaired organelles. Two potential avenues for restoring the ALP function to its physiological state can be considered: enhancing the amount of lysosomes or increasing the functionality of existing lysosomes. First, trehalose emerges as a promising candidate for neuroprotection against various neurodegenerative diseases. This natural disaccharide bears a twofold nature: an mTOR-independent ALP biogenesis enhancer and a chemical chaperone. Second, we previously demonstrated that the use of acidic nanoparticles (aNPs) made of poly (acid lactic-co-glycolic) (PLGA) could restore lysosomal pH through the hydrolytic chain scission of PLGA, providing lactic and glycolic acid units and function in several experimental models of lysosomal impairment. In this study, we have pioneered the development of novel nanovector-based therapies, merging two molecules within a polymersome structure to cross the blood-brain barrier (BBB) and target dopaminergic neurons. We exploited the inherent properties of polymersomes as both nanocarriers and active agents to address acidification defects and potentially restore cellular function coupled with trehalose-based derivatives. The goal is, therefore, to study these dual-targeting nanovectors and their ability to modulate the ALP. In vitro, neuronal cultures will be treated with those NPs to validate their functional effects. In parallel, different routes of administration of these NPs will be tested in vivo (i.e., intracerebral, retro-orbital, and intranasal injections) on mice to assess brain biodistribution and internalization within dopaminergic neurons. These data suggest that strategies enhancing or restoring lysosomal-mediated degradation appear as tantalizing neuroprotective/disease-modifying therapeutic strategies and would be of major interest for PD.

JADOT Hugo (*hugo.jadot@u-bordeaux.fr*).

2024-2025: Engineer, IMN (Institute of Neurodegenerative diseases) - Team 1 Pathophysiology of proteinopathies – Bordeaux

2023-2024: Master 2, Biotechnologies; Applied Neuroscience & Physiology – Faculty of Science and Technology; Nancy

2022-2023: Master 1, Cellular biology and Physiology – Faculty of Science and Technology; Nancy

2019-2022: Bachelor's Degree, Cellular biology and Animal Physiology – Faculty of Science and Technology; Nancy

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3RD THIRD «PHYSIOPATHOLOGY OF PARKINSON'S DISEASE » (HOPE) MEETING BORDEAUX, JANUARY 29-31, 2025

Role of Arkypallidal neurons in motor symptoms of Parkinson's Disease and Levodopa-Induced Dyskinesia

Léa Bonamy[1], Lise Guilhemsang[1], Zhara Ghasemi[1], Nicolas Mallet[1], Jérôme Baufreton[1]
1) Université de Bordeaux, CNRS, IMN, UMR5293, Bordeaux, FRANCE

The external part of the Globus Pallidus (GPe) is part of the basal ganglia motor circuit and is known for its role in relaying information within the indirect pathway. This structure is composed mainly of GABAergic neurons, which are divided into two types: prototypical (PRO: 70%) and arkypallidal (ARKY: 20%) neurons differentiated by their molecular and electrophysiological signatures. Our team has recently shown that optogenetic activation of ARKY neurons inhibits ongoing action, suggesting that this cell type plays a key role in movement control. However, little is known about the contribution of ARKY neurons in the pathophysiology of PD. We first monitored the calcium activity of ARKY neurons in behaving mice longitudinally across three physiopathological conditions: control, parkinsonian-like (PARK), and Levodopa-induced-dyskinesia (DYSK). Our results revealed a complete silencing of ARKY neurons during dyskinesia, while their activity was significantly increased in the PARK condition. ARKY neurons exhibit a specific projection pattern, targeting the striatum exclusively and extensively (**1**), where they deliver a robust stop signal to interrupt the ongoing action (**2**). Our *in vivo* results indicate that ARKY neurons send a strong stop signal during the hypokinetic state (PARK condition), whereas this signal is completely absent during the hyperkinetic state (DYSK condition). To further investigate the alterations of ARKY neurons under these pathological states, we assessed their intrinsic excitability and examined their input connectivity *ex vivo* in acute brain slices through combined patch-clamp and optogenetic approaches. Our findings demonstrate that both the excitability and synaptic connectivity of ARKY neurons are disrupted in pathological conditions. Thus, our findings provide deeper insight into circuit alterations underlying motor symptoms in PD.

(1) Mallet N, Pogosyan A, Márton LF, Bolam JP, Brown P, Magill PJ. Parkinsonian beta oscillations in the external globus pallidus and their relationship with subthalamic nucleus activity. J Neurosci. 2008 Dec 24;28(52):14245-58. doi: 10.1523/JNEUROSCI.4199-08.2008. PMID: 19109506; PMCID: PMC4243385.

(2) Aristieta A, Gittis A. Distinct globus pallidus circuits regulate motor and cognitive functions. Trends Neurosci. 2021 Aug;44(8):597-599. doi: 10.1016/j.tins.2021.06.001. Epub 2021 Jun 15. PMID: 34144845; PMCID: PMC8562495.

Authors Fun Fact :

Lise Guilhemsang: Post-doctoral Researcher in Team 4 (IMN) directed by Nicolas Mallet and Arhtur Leblois.
No, Lise isn't Europe's biggest cotton candy eater—she's a highly respected scout leader in her community!

Nicolas Mallet: Team 4 (IMN) Co-Leader
Without Nico, my thesis topic wouldn't be the same today! He gave the arkypallidal neuron its nickname. Ancient Greek, 'Arky' refers to a type of fishing net, which intriguingly resembles the shape formed by the projections of Arky neurons in the striatum.

Jérôme Baufreton: Bordeaux Neurocampus Director and DNA Team Co-Leader.
His secret recipe for being the best PhD supervisor at Bordeaux Neurocampus? A balanced life fueled by his stress-relief moments in sports like boxing and rugby!

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Léa Bonamy (*lea.bonamy@u-bordeaux.fr*).

I'm a 4th Year in the DNA team at the IMN, led by Dr. Jérôme Baufreton (thesis supervisor) and Dr. François Georges. After an internship in clinical research at Gabriel Montpied Hospital (Clermont Ferrand) in the neurology department working with Parkinson's disease patients, and another internship in my current team focusing on neuronal developmental alterations in Huntington's disease, I started my thesis under Jérôme's supervision.

In addition to my thesis, I have also taught undergraduate students, was a member if the doctoral school council and participated in numerous science popularization events (such as Ma thèse en 180s, Interview for the association Thès'en Images assocation, Podcast Thèse et Vous, Circuit Scientifique Bordelais...)

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Identification of new candidate genes involved in autosomal recessive forms of Parkinson's disease

Tesson C[1], Welment L[1], Cogan G[1], Kodjovi G[1], Honoré A[1], Drouet V[1], Lesage S[1], Brice A[1]
1) Sorbonne Université, Institut du Cerveau - Paris Brain Institute - ICM, Inserm, CNRS, APHP, Hôpital de la Pitié Salpêtrière, Paris, France

Parkinson disease (PD) affects 1-2% of the population above 65 years. It is characterized by the triad of symptoms: tremor, rigidity, and bradykinesia. To date, more than 10 validated genes have been identified, associated with either autosomal dominant (AD) or autosomal recessive (AR) forms of PD. However, the identified genes associated with early-onset (EO, <40 years) AR PD only explains 45%, other genes remain to be discovered. The aim of the work is to identify new genes involved in EO AR PD, using consanguineous PD families and applying genotyping on DNA microarrays, homozygosity mapping and NGS technologies.
To identify new genes involved in EO-AR PD, we performed whole exome sequencing (WES) on a cohort of 1244 patients (1100 index cases) presenting early onset sporadic PD or AR-PD. At first, we focused on loss of function variants (LoF) identified in the cohort, and/or genes presenting variants in at least 2 unrelated families.
This strategy enabled us to identify 25 candidate genes with LoF variants in 27 families, as possibly being involved in PD. Among them, we identified the homozygous p.Asp38Ilefs*7 frameshift variant in *CISD1* in a consanguineous family. This variant is absent from the GnomAD database. In silico analysis predicts this variant to induce transcript degradation by the Nonsense Mediated Decay. Interestingly, CISD1 was identified as a major target of PINK1/Parkin complex, moreover the KO mouse model presents a decreased level of dopamine in the striatum and locomotor abnormalities in the rotarod test.
Further functional data are needed to strengthen the role of *CISD1* as well as that of other genes carrying identified LoF variants associated with EO AR PD. The functional validation will be tested by inactivation of these genes on simple organisms, i.e. drosophila melanogaster and C. elegans, to look for induced-locomotor defects.
…
…

Presenter name (*Christelle.tesson@icm-institute.org*). After a PhD at the Institut du Cerveau on the genetic and functional characterization of a new gene for hereditary spastic paraplegia CYP2U1/SPG56, Dr. Tesson contributed to research on mitochondrial respiratory chain deficiencies as an engineer. (INSERM UMR_S 1124).

Since February 2016, she has been a dedicated and experienced researcher specializing in neurogenetics and molecular biology, working as a postdoctoral researcher at the Brain Institute, focusing on the identification of new genes involved in Parkinson's disease. Her work has contributed to the validation of the involvement of *DAGLB* in Parkinson's disease, as well as the identification of *PTPA* and *PSMF1* in the pathology.

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3RD THIRD «PHYSIOPATHOLOGY OF PARKINSON'S DISEASE » (HOPE) MEETING BORDEAUX, JANUARY 29-31, 2025

The Chaperone DNAJB6 Inhibits aSyn Aggregation in Models of Induced Synucleinopathy

Ænora Letourneur[1,2], Hortense de la Seglière[2], Marianna Kashyrina[3], Francesco De Nuccio[3], Nathalie Dutheil[2], Marie-Laure Thiolat[2], Leslie-Ann Largitte[2], Ludivine Sabatier[2], Florent Laferrière[2], Marion Psomiades[1], Elodie Angot[4], Dario Domenico Lofrumento[3], Francesca De Giorgi[2], François Ichas[2]

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2. *University of Bordeaux, IMN, CNRS UMR5293, Bordeaux, France*
3. *University of Salento, I-73100 Lecce, Italy*
4. *Roche Pharma Research and Early Development, Roche Innovation Center Basel, F.Hoffmann-La Roche Ltd, Basel, Switzerland*

Parkinson's disease is an α-Synucleinopathy in which neurodegeneration is linked to the appearance and intracerebral spread of intracellular aggregates, populated by self-replicating amyloid fibrils made of α-Synuclein (α-Syn)[1]. The chaperone DNAJB6 has been shown to inhibit polyglutamine protein aggregation, and recently, to have the same effect on aSyn aggregation, in cell lines[2,3]. We investigated that effect in neurons, in two models of induced synucleinopathy: in primary cultures of mouse cortical neurons, and *in vivo*, in wild-type adult mice. Endogenous aSyn aggregation was induced by introducing pre-formed fibrils (PFFs), in the culture medium of the primary culture, or by intrastriatal injection *in vivo*. DNAJB6 overexpression was induced by infection with a DNAJB6 AAV, directly in the culture medium or by injection in the *substantia nigra in vivo*. Neo-formed aggregates as well as the overexpressed chaperone were imaged using double immunofluorescence detection. The overexpression of DNAJB6 led to a reduced aggregation, both in cultures and *in vivo*. We explored what mechanisms lay behind this effect of DNAJB6 overexpression. We had three hypotheses: DNAJB6 binds the aSyn monomer and prevents it from being recruited into the fibril; DNAJB6 binds the fibrils and prevents their growth; or DNAJB6 disaggregates the fibrils as part of a chaperone system usually containing DNAJB1. We investigated the first two hypotheses with an immunocapture aSyn pre-incubated with DNAJB6, and found that DNAJB6 interacts with aSyn fibrils, but not with monomers. For the third hypothesis, we tested the effect of the chaperone system on the fibril, as is or with DNAJB6 replacing DNAJB1, by measuring the released monomeric aSyn, in Western Blot. We found that replacing DNAJB1 with DNAJB6 severely decreases the disaggregation effect, leading us to believe the impact of the overexpression of DNAJB6 on the synucleinopathy is not due to its involvement with the chaperone system.

1. *Spillantini, M. G. et al. α-Synuclein in filamentous inclusions of Lewy bodies from Parkinson's disease and dementia with Lewy bodies. Proc. Natl. Acad. Sci. U. S. A.* ***95****, 6469–6473 (1998).*
2. *Hageman, J. et al. A DNAJB Chaperone Subfamily with HDAC-Dependent Activities Suppresses Toxic Protein Aggregation. Mol. Cell* ***37****, 355–369 (2010).*
3. *Deshayes, N. et al. The Molecular Chaperone DNAJB6, but Not DNAJB1, Suppresses the Seeded Aggregation of Alpha-Synuclein in Cells. Int. J. Mol. Sci.* ***20****, 4495 (2019).*

Microglia-enriched human midbrain organoids for studying Parkinson's disease

Helena Winterberg[1], Benjamin Galet[1], Jana Heneine[1], Adeline Muscat[1], Anaelle Pincon[1], Pauline Lachal[1], Julie Smeyers[1], Morwena Latouche[1], Philippe Ravassard[1], Olga Corti[1]

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Parkinson's disease (PD) patients display signs of activated microglia, the resident immune cells of the central nervous system. The precise interplay between neuronal and microglial cells, and how it affects the vulnerable dopaminergic neurons in PD, remains to be determined. Region specific organoids, which lack microglial cells due to their yolk-sac origin, provide a platform for studying underlying disease mechanism. Our objective is to study how microglial cells impact dopaminergic neuron maturation following incorporation into human midbrain-specific organoids (hMO), and to explore the impact of loss-of-function (KO) mutations in *PRKN*, a gene responsible for autosomal recessive forms of PD. We generated human microglia-like cells from peripheral blood-derived monocytes (MDMi) or primitive macrophages (iMACs) from induced pluripotent stem cells (iPSC), the latter recapitulating the developmental origin of tissue-specific macrophages. Specifically, MDMi were differentiated from peripheral blood monocytes cultured for two weeks in the presence of IL-34 and GM-CSF (Sellgren et al., 2017), while iMACs were derived from iPSCs within 26 days (Takata et al., 2017). In Gene set enrichment analyses (GSEA), we observed increased expression of genes related to endoplasmic reticulum stress and cellular response to misfolded proteins in MDMi with *PRKN* mutations compared to control cells, at baseline. Proinflammatory stimulation with lipopolysaccharide (LPS), in presence or absence of the NLRP3 inflammasome activator 2'(3')-O-(4-benzoylbenzoyl)-adenosine-5'-triphosphate (BzATP) increased additionally the expression of genes related to Golgi vesicle transport pathways. Next, we explored the impact of these altered responses on a 3D midbrain-like neuronal environment. At day 30 of co-culture the MDMi and iMACs acquired ramified microglia-like morphologies within the 3D structures of the organoids and represented around 1-2% of the total cell population in control organoids. This percentage dropped to 0.5% on a *PRKN* KO background, demonstrating less efficient integration of iMACs compared to controls. Co-culturing control organoids with iMACs led to an increase in the proportion of NeuN+ neuronal nuclei in the 3D environment, an effect that was not observed in the *PRKN*-KO organoids. The number of dopaminergic neurons remained unaffected in both conditions. As a perspective, the hMO model will be extended to incorporate patient-derived microglia-like cells.

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3RD THIRD «PHYSIOPATHOLOGY OF PARKINSON'S DISEASE » (HOPE) MEETING BORDEAUX, JANUARY 29-31, 2025

Urinary proteome profiling in rats and humans unveils biomarkers of LRRK2 kinase activity in Parkinson's disease

Jean-Marc Taymans[1], Duc Tung Vu[2*], William Sibran[1], Laurine Vandewynckel[1], Liesel Goveas[1], Claire Deldycke[1], Adriana Figueroa-Garcia[1], Andreas Metousis[2], Basak Eraslan[3], Ericka Corazon Itang[2], Johannes Bruno Müller-Reif[2], Sebastian Virreira Winter[2], and Matthias Mann[2*], Ozge Karayel[2,4*], Marie-Christine Chartier-Harlin[1*]*

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[2]Department of Proteomics and Signal Transduction Max Planck Institute of Biochemistry Martinsried Germany
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**equal contributions*

Pathogenic mutations in Leucine-rich repeat kinase 2 (LRRK2) are the predominant genetic cause of Parkinson's disease (PD) and often lead to increased kinase activity, making LRRK2 inhibitors promising treatment options. However, despite ongoing clinical trials, reliable biomarkers for tracking drug engagement or identifying mutation carriers are lacking. Analyzing urinary proteomes from 1,215 individuals with PD and/or LRRK2 mutations across three cohorts, we identified 177 significantly altered urinary proteins linked to dysregulation of immune system processes, membrane trafficking, and lysosomal-glycosphingolipid metabolism in pathogenic LRRK2 carriers. Machine learning narrowed these features down to a cohort-agnostic panel of 30 key urinary proteins—primarily associated with lysosomal dysfunction—offering a robust readout of LRRK2 activity. Our model excelled in classifying mutation status, achieving an ROC AUC of 0.91, 88% sensitivity, and 80% specificity. Urinary profiling in rats treated with LRRK2 inhibitors further validated the panel's ability to monitor pharmacodynamic responses to LRRK2 inhibitors in clinical practice. Our panel of biomarker candidates could play a crucial role in assessing LRRK2 hyperactivation and inhibition, supporting future PD therapies focused on restoring LRRK2's normal physiological function.

Jean-Marc Taymans (*jean-marc.taymans@inserm.fr*). Dr. Taymans is currently associate Professor in Neuroscience at the Lille Neuroscience & Cognition Research Center (Inserm, Université de Lille, CHU Lille, Lille, France). He holds a masters in Bio-Engineering (KU Leuven, Belgium), a diploma in international relations (UCLouvain, Belgium), a PhD in neurosciences (VU Amsterdam, Netherlands) as well as a research habilitation degree (HDR, Université de Lille, France). His research priority since 20 years is the study of signaling properties of Parkinson's disease proteins, with a focus on LRRK2.

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Abstract should be one page max (all texts and references). No Figure.

Glucocorticoid receptors in astrocytes regulate alpha-synuclein pathological actions impacting motor an non-moto symptomology of Parkinson's disease.

Chaperon A[1], Compagnion A-C[1], Bhattacharya S1, Vernochet C[1], Poysti A, Anand R, Brouillet[2], Tronche F[1], Parnaudeau S[1], NAthalie Rouach[3], Dongdong Li[4], Bemelmans[2], Vyas S[1].

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4. Neuroglial Interactions in Cerebral Physiology and Pathologies laboratory, Center for Interdisciplinary Research in Biology, Collège de France

Our research is focused on the role glucocorticoids (GC) and its receptor GR in Parkinson disease (PD) pathology. PD is characterized by degeneration of dopamine neurons, presence of Lewy Bodies containing pathological alpha-synuclein and chronic inflammation. Alpha-synuclein pathology affects both motor symptoms and non-motor symptoms of PD. GC-GRs not only regulate inflammation but profoundly modulate mood and cognition. Death of dopamine neurons in substantia nigra results in characteristic motor symptoms in PD. To study the role of astrocyte GC-GR in PD, we are using mice conditionally inactivated for GR gene specifically in parenchymal astrocytes. Stereotaxic injection of AAV human A53T alpha-synuclein viral vector in substantia nigra of control and astrocyte GR mutant mice resulted, after 8 weeks, in greater dopamine neuronal loss with increased glial reactivity in astrocytic GR mutant mice, suggesting astrocyte GR modulates alpha-synuclein pathology and likely motor symptoms. We first evaluated non-motor symptoms of PD - anxiety, depression, social interaction and cognition - in C57/BL6 mice injected with AAV human A53T alpha-synuclein viral vector either in Ventral Tegmentum Area (VTA) or in prefrontal cortex. Mood or cognitive deficits were not induced by A53T alpha-synuclein pathology in wild type mice. Next we analyzed whether astrocytic GR mutant mice have behavioral, cognitive or motor anomalies. The results showed increased anxietylike behavior and reduced motor performance in astrocytic GR mutant mice with no change observed in cognitive tests. Interestingly, expression of A53T alpha-synuclein in prefrontal cortex of astrocytic GR mutant and control mice resulted in impairment of working memory only in the GR mutant mice. We are investigating the cellular and biochemical mechanisms through which astrocyte GR regulates cognitive processes in face of alpha-synuclein pathology.

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3RD THIRD «PHYSIOPATHOLOGY OF PARKINSON'S DISEASE » (HOPE) MEETING BORDEAUX, JANUARY 29-31, 2025

Transcriptional Regulation of α-synuclein Expression by TRIM17/TRIM41/ZSCAN21 pathway in Parkinson's disease

Alina Kozoriz[1], Stephan Mora[1], Suzanne Lesage[2], Miquel Vila[3], Solange Desagher[1,4] and Iréna Lassot[1]**

1)Institut de Génétique Moléculaire de Montpellier; CNRS, Univ. Montpellier; Montpellier 34293, France.
2) Sorbonne Universités, UPMC Univ Paris 06, UMR S 1127, Institut du Cerveau et de la Moelle épinière, ICM, Paris, France; INSERM U 1127; CNRS UMR 7225, AP-HP, Pitié-Salpêtrière Hospital, Paris, France.
3) Neurodegenerative Diseases Research Group, Vall d'Hebron Research Institute-Center for Networked Biomedical Research on Neurodegenerative Diseases (CIBERNED), 08035 Barcelona, Spain.
4) Current address: Institut de Recherche en Infectiologie de Montpellier; CNRS, Univ. Montpellier; Montpellier 34293, France.

Both inherited and sporadic forms of Parkinson's disease (PD) can be due to increased expression of α-synuclein. However, despite its crucial role in the pathogenesis of PD, the mechanisms regulating the transcription of *SNCA* gene are mostly unknown. We have identified a new pathway regulating α-synuclein expression involving the transcription factor ZSCAN21 and two E3 ubiquitin-ligases TRIM17 and TRIM41. Indeed, we have shown that ZSCAN21 induces the expression of α-synuclein and that its stability is regulated by TRIM41 which induces the ubiquitination and proteasomal degradation of ZSCAN21, and by TRIM17 which stabilizes ZSCAN21 by inhibiting TRIM41. Our results in a cellular model of PD revealed several regulatory elements in *SNCA* locus, mostly activated upon MPP^+ treatment and where ZSCAN21 can bind. We also reported that an increase in the mRNA levels of Zscan21 and Trim17 is concomitant with the peak of α-synuclein expression in the midbrain of mice following MPTP treatment, whereas a decrease in Trim41 precedes it (1). Moreover, we found that silencing of Zscan21, using shRNA-expressing adeno-associated virus (AAV) injected in the Substantia Nigra (SN), significantly protected DA neurons from MPTP-induced neurodegeneration compared to mice injected with control shRNAs. In parallel, we have identified rare variants of *TRIM17*, *TRIM41* and *ZSCAN21* genes in patients with autosomal dominant Parkinson's diseases (PD), two of which co-segregate with the disease (1). Interestingly, another study has identified disrupting variants of ZSCAN21 in patients with familial PD, that co-segregate with the disease (2). Taken together, our data suggest that a dysregulation of TRIM17/TRIM41/ZSCAN21 pathway may be involved in the pathogenesis of PD by increasing the expression of α-synuclein.

1. I. Lassot et al., *Cell Rep.* 2018 Nov 27;25(9):2484-2496.e9
2. A. Gialluisi et al. *Molecular Neurodeg.* Jun 21;16(1):35 (2021).

NB.
Abstract should be one page max (all texts and references). No Figure.

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Irena Lassot (*irena.lassot@igmm.cnrs.fr*). I am a researcher in the instute of molecular genetics in Montpellier. I am interested in the molecular mechanisms involved in the abnormal expression of certain genes and in the deregulation of signaling pathways involved in the pathogenesis of Parkinson's Disease, more specifically the pathways involving TRIM17, TRIM41 and ZSCAN21.

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