**BIOGRAPHICAL SKETCH**

NAME: Lies DE GROEF

POSITION TITLE: Assistant Professor

EDUCATION/TRAINING

| INSTITUTION AND LOCATION | DEGREE | Completion Date | FIELD OF STUDY |
|---|---|---|---|
| KU Leuven, Group Science & Technology, Belgium | Ba | 07/2008 | Biochemistry & Biotechnology |
| KU Leuven, Group Science & Technology, Belgium | Ma | 07/2010 | Biochemistry & Biotechnology, Animal Physiology |
| KU Leuven, Group Science & Technology, Belgium | Ph.D. | 06/2015 | Neuroscience |
| University College London, Institute of Ophthalmology, United Kingdom | PD fellow | 12/2016 | Ophthalmology, Neuroscience |
| KU Leuven, Group Science & Technology, Belgium | PD fellow | 01/2022 | Neuroscience |

**A. Personal Statement**

During my PhD, I have been investigating the contribution of matrix metalloproteinases to neurodegeneration, -regeneration and -inflammation in the glaucomatous eye/visual system. Since 2014, I have been closely involved in the establishment of the 'Vision Core Leuven' (www.visioncore.be), which has led to my new focus on state-of-the-art technologies for ocular imaging, electrophysiology and visual function testing. Pursuing this career turn, I've completed a one-year training in the Glaucoma and Retinal Neurodegenerative Disease Research Group at University College London (London, UK) to become an expert in *in vivo* imaging techniques to follow eye pathology in rodents (confocal ophthalmoscopy, optical coherence tomography, detection of apoptosing retinal cells).

Since 2021, I'm heading the Cellular Communication and Neurodegeneration research group (Biology Department, KU Leuven). which works at the cross-over of neurobiology and ophthalmology, and exploits this combination of disciplines to enrich fundamental research into central nervous system (CNS) function. A greater understanding of the cellular and molecular mechanisms governing brain function are key to unlock novel therapeutic strategies for CNS diseases – which represent a rising burden –, and the visual system offers unique possibilities to tackle these research questions. Focusing on the retina-brain axis, we unravel mechanisms of neuron-glia communication in the CNS, with a focus on the role of extracellular vesicles as messenger and transport organelles in neuro-inflammation and protein propagation. We study these interactions both under physiological conditions and in the context of Parkinson's, Alzheimer's disease and Wolfram syndrome.

This research approach is founded on a strong knowledge base of neurodegeneration and -inflammation research in the visual system, in vivo retinal imaging, electrophysiology and visual behavior testing, and expertise in rodent disease models of neurodegenerative diseases, primary retinal cell cultures and organotypic explants. Our research is primarily focused on the fundamental study of the cell biology of neurodegeneration. However, in addition, we also have developed an interest in patient and post mortem studies, to investigate the use of retinal manifestations as biomarkers for detection of neurodegenerative proteinopathies.

**B. Positions and honors**

**Positions and employment**

| | |
|---|---|
| 2021- | Assistant Professor (BOFZAP), Cellular Communication and Neurodegeneration Research Group, University of Leuven, Belgium & Research Foundation Flanders |
| 2019-2022 | Senior Postdoctoral Research Fellow, Neural Circuit Development and Regeneration Research Group, University of Leuven, Belgium & Research Foundation Flanders |
| 2016-2019 | Postdoctoral Research Fellow, Neural Circuit Development and Regeneration Research Group, University of Leuven, Belgium & Research Foundation Flanders |
| 2016 | Postdoctoral Research Fellow, Glaucoma and Retinal Neurodegenerative Disease Research Group, Institute of Ophthalmology, University College London, UK |
| 2010-2015 | PhD student, Neural Circuit Development and Regeneration Research Group, University of Leuven, Belgium & Flemish Government Agency for Innovation by Science and Technology |

**Other experience and Professional Memberships**

- Review Editor, Frontiers in Neuroscience, Neurodegeneration Section; Guest Editor, International Journal of Molecular Sciences, special issue "Molecular Mechanisms of Neural Circuit Development and Regeneration"; Solicited Reviewer for various journals (Acta Neuropathologica, Investigative Ophthalmology and Visual Science, Experimental Eye Research, BMC Ophthalmology, Neural Regeneration Research, Scientific Reports); Reviewer, UK Medical Research Council
- Founding member of "The Eye as a Biomarker for AD" Professional Interest Area, Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment (ISTAART); Member of Retinal ganglion cell Repopulation, Stem cell Transplantation, and Optic nerve Regeneration (RReSTORe) consortium (RReSTORe)
- Member of PhD jury of Drs. Charline Borghgraef (KU Leuven), Emma Coninckx (KU Leuven), Charysse Vandendriessche (UGent)
- Member of the organizing committee of the bi-annual Synuclein Meeting, Leuven, Belgium (2022); Organizer and moderator of special interest symposia, Meeting of the European Association for Vision and Eye Research, France (2017 & 2018)
- Lecturer "Science Communication", "Animal Physiology", "Integrated practical course - molecular techniques in functional research", KU Leuven, Belgium
- Member of the Faculty Council, Faculty of Sciences, KU Leuven; Departmental Council, Department of Biology, KU Leuven; Vesalius museum workgroup, KU Leuven; PRICe (Mapping the Perception of Research Integrity Culture at KU Leuven) workgroup, KU Leuven.

Member of the Belgian Society for Extracellular Vesicles (BESEV), International Society for Extracellular Vesicles (ISEV), European Association for Vision and Eye Research (EVER), Association of Research in Vision and Ophthalmology (ARVO), Society for Neuroscience (SfN), Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment (ISTAART).

**Honors and awards**

| | |
|---|---|
| 2020 | Alzheimer's Research Foundation (SAO-FRA), pilot research grant for junior researchers |
| 2016 | Research Foundation Flanders, travel grant for a research stay abroad (for stay at UCL) |
| 2016 | Awarded by the Fund for Research in Ophthalmology, prize Ligue Braille |
| 2015 | Alumni of Botany and Zoology of KU Leuven, triennial prize for most outstanding PhD thesis in Biology |
| 2012 – 2018 | Travel grants from Research Foundation Flanders and Academische Stichting Leuven to attend international scientific meetings (Honolulu, USA; Washington, USA; Denver, USA; Nice, France) |
| 2011 | First prize awarded by the Fund for Research in Ophthalmology |
| 2010 | Royal Flemish Society for Chemistry, award for most commendable graduating biochemistry student |

## C. Contributions to Science

**I.** Retinal manifestations of Parkinson's disease

I consider my major achievement thus far the setting-up of my autonomous research program, focused on alpha-synucleinopathy in the retina/visual system. Although still under the umbrella of the Neural Circuit Development and Regeneration research group, I've set up a research line that is fully independent from that of my PhD promotor. From a scientific point of view, the paper by Normando *et al*., to which I contributed during my postdoctoral fellowship at University College London, was groundbreaking in that it was the first to show retinal alterations in an experimental animal model of Parkinson's disease. Later papers of mine, including the Acta Neuropathologica paper by Veys *et al*., further added to this research line and have helped to establish myself in this field:

- Normando, E.M., Davis, B.M., De Groef, L., Nizari, S., Turner, L.A., Ravindran, N., Pahlitzsch, M., Brenton, J., Malaguarnera, G., Guo, L., Somavarapu, S., Cordeiro, M.F. (2016). The retina as an early biomarker of neurodegeneration in a rotenone-induced model of Parkinson's disease: evidence for a neuroprotective effect of rosiglitazone in the eye and brain. Acta Neuropathologica Communications, 4 (86), 1-15.
- Guo, L., Normando, E.M., Shah, P., De Groef, L.*, Cordeiro, M.F.* (2018). Oculo-visual abnormalities in Parkinson's disease: possible value as biomarkers. Movement Disorders, 33 (9), 1390-1406. (*joint senior authors)

- Veys, L., Vandenabeele, M., Ortuño-Lizarán, I., Baekelandt, V., Cuenca, N., Moons, L., De Groef, L. (2019). Retinal alpha-synuclein deposits in Parkinson's disease patients and animal models. Acta Neuropathologica, 137 (3), 379-395.
- Veys, L., Van houcke, J., Aerts, J., Van Pottelberge, S., Mahieu, M., Bousset, L., Melki, R., Moechars, D., De Muynck, L., De Groef, L. (2020) Absence of uptake and prion-like spreading of alpha-synuclein and tau after intravitreal injection of preformed fibrils. Frontiers In Aging Neuroscience 12, Art.No. 614587.
- Veys, L., Devroye, J., Lefevere, E., Cools, L., Vandenabeele, M., De Groef, L. with De Groef, L. (corresp. author) (2021). Characterizing the Retinal Phenotype of the Thy1-h[A30P]α-syn Mouse Model of Parkinson's Disease. Frontiers In Neuroscience, 15, Art.No. 726476.

**II.** Retinal biomarkers for Alzheimer's diagnosis and research into its preclinical phase

The research paper by Vandenabeele *et al.* is one of my major achievements for two reasons. First, because it is the result of collaborative research in a consortium of national and international partners, with clinicians, scientists and engineers. Since 2016, I have been leading the preclinical mouse work for this project, and I was also (co-)responsible for research coordination and grant writing in this consortium. This led to the adoption of the project by the Mission lucidity initiative (https://www.missionlucidity.com/project/eye-window-brain-1) and recent successful funding applications within 1) the EU Joint Programme – Neurodegenerative Disease Research and 2) the Global PhD Partnership KU Leuven-University of Melbourne. As such, it shows my experience with managing large, multi-partner projects. Second, this manuscript is an exemplification of the strengths of the retina as a model for CNS research. It showcases the quality and quantity of data that can be gathered using in vivo retinal imaging and electrophysiology, and the genericity of these findings (i.e., retinal disease manifestations mirroring those seen in the brain). We believe that this paper will have a large impact on the Alzheimer's research field, as it presents the first animal model for research into the pre-symptomatic, preclinical phase of Alzheimer's. Underscoring the high translational potential of this research, the imaging technology that I implemented during this study was later also used in a pilot clinical trial in AD patients:

- Vandenabeele, M., Veys, L., Lemmens, S., Hadoux, X., Gelders, G., Serneels, L., Theunis, J., De Boever, P., Stalmans, I., De Strooper, B., Van Wijngaarden, P., Moons, L., De Groef, L. (2020) The APP NLGF mouse retina is a site for preclinical Alzheimer's disease diagnosis and research. Acta Neuropathologica Communications, 9, Art.No. 6.
- Lemmens, S., Van Craenendonck, T., Van Eijgen, J., De Groef, L., Bruffaerts, R., Andrade de Jesus, D., Charle, W., Jayapala, M., Sunaric-Mégevand, G., Standaert, A., Theunis, J., Van Keer, K., Vandenbulcke, M., Moons, L., Vandenberghe, R., De Boever, P., Stalmans, I. (2020) Combination of snapshot hyperspectral retinal imaging and optical coherence tomography to identify Alzheimer's disease patients. Alzheimer's Research & Therapy, 12 (1), Art.No. 144.

**III.** Neuron-glia communication in the retina

A third achievement is one of my latest papers in Glia. In this study, which was founded on results that I gathered during my PhD and later, under my supervision, completed by PhD student E. Lefevere (co-promotor), we disentangled the complex interplay between neurons and glia at the blood-retinal barrier. It adds new evidence to the biological phenomenon of blood-retinal (or brain) barrier tightening, which – in contrast to the opposite process of disruption – is barely studied in the CNS and may be a missing link in our understanding of the physiology/pathology of the CNS neurovascular unit. This paper reflects my research focus on neuron-glia interactions in the CNS. In fact, it should be considered together with multiple others, including those that resulted from my PhD research (cfr. below for a selection). Together, they illustrate my broad expertise in neurodegeneration and -inflammation research in the mouse visual system, which forms the basis of my future research plans:

- Lefevere E.*, Salinas-Navarro M.*, Andries L., Noterdaeme L., Etienne I., Van Wonterghem E., Davis BM., Van Bergen T., Vinkier S., Van Hove I., Movahedi K., Vandenbroucke RE., Moons, L.*, De Groef L.* (2020). Tightening the retinal glia limitans attenuates neuroinflammation after optic nerve injury. Glia, 68(12), 2643-2660. (*joint senior authors)
- De Groef, L., Andries, L., Siwakoti, A., Geeraerts, E., Bollaerts, I., Noterdaeme, L., Etienne, I., Papageorgiou, A-P., Stalmans, I., Billen, J., West-Mays, J.A., Moons, G. (2016). Aberrant Collagen Composition of the Trabecular Meshwork Results in Reduced Aqueous Humor Drainage and Elevated IOP in MMP-9 Null Mice. Investigative Ophthalmology & Visual Science, 57 (14), 5984-5995.
- De Groef, L.*, Dekeyster, E.*, Geeraerts, E., Lefevere, E., Stalmans, I., Salinas-Navarro, M., Moons, L. (2016). Differential visual system organization and susceptibility to experimental models of optic

neuropathies in three commonly used mouse strains. Experimental Eye Research, 145, 235-247. (*joint first authors)
- Dekeyster, E., Geeraerts, E., Buyens, T., Van Den Haute, C., Baekelandt, V., De Groef, L., Salinas-Navarro, M., Moons, L. (2015). Tackling Glaucoma from within the Brain: An Unfortunate Interplay of BDNF and TrkB. PLoS One, 10 (11), 1-28.
- De Groef, L., Salinas Navarro, M., Van Imschoot, G., Libert, C., Vandenbroucke, R., Moons, L. (2015). Decreased TNF levels and improved retinal ganglion cell survival in MMP-2 null mice suggest a role for MMP-2 as TNF sheddase. Mediators of Inflammation, 2015 (2015).

**IV.** Image analysis tools to study retinal neurodegeneration and -inflammation
I published a series of papers (cfr. below) dedicated to the development and validation of image analysis methods to study retinal neurodegeneration and -inflammation, which are essential tools for the research that I'm conducting. The goal of these is to maximize the information extracted from microscopy images via a combination of classic imaging analysis techniques and advanced statistics and/or deep learning. All of these tools are freely available as user-friendly software, as part of my commitment to supporting open science. This research has been propelled by a collaboration with Dr. B. Davis, that I've initiated during my postdoctoral fellowship at University College London, and that still lasts up till today.
- Davis, M.B., Guo, L., Ravindran, N., Shamsher, E., Baekelandt, V., Mitchell, H., Bharath, A.A., De Groef, L.*, Cordeiro, M.F.* (2020) Dynamic Changes in Cell Size and Corresponding Cell Fate After Optic Nerve Injury. Scientific Reports, 10 (1), Art.No. 21683.
- Masin, L., Claes, M., Bergmans, S., Cools, L., Andries, L., Davis, B.M., Moons, L., De Groef, L. (2020) RGCode: a novel Retinal Ganglion Cell quantification tool based On DEep learning. Scientific Reports, 11 (702).
- Davis, B.M., Salinas-Navarro, M., Cordeiro, M.F., Moons, L., De Groef, L. (2017). Characterizing microglia activation: a spatial statistics approach to maximize information extraction. Scientific Reports, 7, Art.No. 1576.
- Geeraerts, E., Dekeyster, E., Gaublomme, D., Salinas Navarro, M., De Groef, L., Moons, L. (2016). A freely available semi-automated method for quantifying retinal ganglion cells in entire retinal flatmounts. Experimental Eye Research, 147, 105-113.

**V.** As a final achievement, I've chosen the scRNAseq study that I recently conducted, in collaboration with Oxurion NV (Leuven) and the Laboratory of Translational Genetics (VIB-KU Leuven). In this study, we specifically focused on the phenotypic changes in retinal macroglia in response to diabetic retinopathy and identified several subpopulations of astrocytes/Müller glia that specialize to perform distinct functions in the diabetic retina. As such, this study contributes to a better understanding of glia biology in the retina. Notably, this scRNAseq study was the first performed within the KU Leuven Biology department. Hence, besides my excellent relations with industry (here the biopharma company Oxurion), this paper shows my ability to adopt new technologies by engaging in collaborations with experts in different fields and my standing expertise in scRNAseq data analysis.
- Van Hove, I.*, De Groef, L.*, Boeckx, B., Modave, E., Hu, T., Beets, K., Etienne, I., Van Bergen, T., Lambrechts, D., Moons, L., Feyen, J., Porcu, M. (2020). Single-cell transcriptomics analysis of Akimba retina reveals cell type-specific insights into the pathology of diabetic retinopathy. Diabetologia, 63(10), 2235-2248. (*joint first authors)

My scientific output consists of +55 papers and book chapters in peer-reviewed international journals. This work resulted in an h-index of 17 and a total of 728 citations (no self-citations; Web of Science; January 2022). For a complete publication list and an additional list of papers presented at international meetings please see: https://lirias.kuleuven.be/cv?u=U0073996

## D. Research Support and Scholastic Performance

**Ongoing Research Support**

Alzheimer's Research Foundation (SAO-FRA) 2022 – 2024
"Hyperspectral retinal imaging as a novel diagnostic biomarker for Alzheimer's disease"
Role: PI Goal: Preclinical and clinical research into retinal hyperspectral imaging for Alzheimer's diagnosis

FWO fellowship to Drs. Lien Cools 2021 – 2025
"Unravelling the role of extracellular vesicles in Parkinson's pathogenesis: nano-organelles with mega impact?"

Role: Promotor Goal: Study the role of extracellular vesicles in neuroinflammation and protein aggregation/propagation in Parkinson's disease

FWO SB fellowship to Drs. Karan Ahuja 2021 – 2025
"Unravelling neuron-glia interactions in Wolfram syndrome through optic nerve-on-chip and in vivo base editing"
Role: Co-promotor Goal: Understand the differential contribution of neurons versus glia to Wolfram syndrome and develop a gene therapy

C3/21/012 KU Leuven 2021 – 2023
"A killifish R&D platform for therapies improving healthy brain aging"
Role: co-PI Goal: Establish a research platform for gerontology research in vertebrates

Research Foundation Flanders, project funding (G049321N) 2021 – 2024
"Cell-type-specific omics to understand cellular recycling in ageing"
Role: co-PI Goal: Study cellular recycling in ageing in C. elegans

Global PhD Partnership KU Leuven - University of Melbourne (2 joint PhD projects) 2021 – 2024
"The eye as a window to the brain: tackling neurodegenerative disorders"
Role: co-PI Goal: Preclinical and clinical research into retinal biomarkers for Alzheimer's diagnosis

EU Joint Programme - Neurodegenerative Disease Research 2021 – 2023
"Global retinal imaging consortium for Alzheimer's disease (BRAINSTORM)"
Role: partner Goal: Preclinical and clinical research into retinal biomarkers for Alzheimer's diagnosis

Central Europe Leuven Strategic Alliance (CELSA) 2020 – 2022
"Ferroptosis: a novel paradigm in the neurodegenerative pathology of Wolfram syndrome"
Role: co-PI Goal: Study ferroptosis as a disease mechanism underlying Wolfram syndrome, with a focus on the visual system

Alzheimer's Research Foundation (SAO-FRA) 2020 – 2022
"A preclinical research platform for Alzheimer's disease in the eye"
Role: PI Goal: Validation of the retina and retinal imaging/electrophysiology read-puts for preclinical research in mouse models of Alzheimer's disease

Queen Elisabeth Medical Foundation 2020 – 2022
"Oligodendrocytes in Wolfram syndrome: bystanders or partners in crime?"
Role: co-PI Goal: Study the differential contribution of neurons *versus* oligodendrocytes to Wolfram syndrome pathogenesis in iPSC and mouse models

FWO fellowship to Drs. Marjan Vandenabeele 2019 – 2023
"Unraveling the importance of oligodendrocytes in neurodegeneration: a new look on Wolfram syndrome."
Role: co-promotor Goal: Study the differential contribution of neurons *versus* oligodendrocytes to Wolfram syndrome pathogenesis in iPSC and mouse models

C14/18/053 KU Leuven 2018 – 2022
"Intra-neuronal energy channeling: a prerequisite for functional CNS repair"
Role: co-PI Goal: Investigation of the cellular metabolic processes driving axonal regeneration in the mammalian visual system

FWO SB fellowship to Drs. Lien Veys 2018 – 2022
"The eye as a window to the brain: modulating neuroinflammation to halt retinal alpha-synucleinopathy"
Role: co-promotor Goal: Investigation of the impact of alpha-synucleinopathy on the retina, with a special focus on neuro-inflammation, in newly developed mouse models

1526218N Research Foundation Flanders 2018 – 2020
"The eye as a window to the brain: new look on Alzheimer's and Parkinson's disease."
Role: PI Goal: Investigation of the retina and retinal imaging/electrophysiology read-puts for preclinical research in mouse models of Alzheimer's and Parkinson's disease

G053217N Research Foundation Flanders 2017 – 2020
"Neuroinflammation as motor for axonal regeneration: a quest for underlying molecular players"
Role: co-PI Goal: Study of the molecar players driving axonal regeneration in the mammalian visual

**Scholastic Performance**

- Training and supervision of >20 bachelor and master students, Faculty of Sciences, Department of Biology, KU Leuven, Belgium
- Supervision of 7 PhD students (4 ongoing, 3 completed), Faculty of Sciences, Department of Biology, KU Leuven, Belgium