BIOGRAPHICAL SKETCH

NAME: Lieve (Godelieve) MOONS

POSITION TITLE: Full Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
KU Leuven, Group Science & Technology, Belgium	Ba	07/1982	Biology
KU Leuven, Group Science & Technology, Belgium	Ma	07/1984	Biology, Animal Physiology
KU Leuven, Group Science & Technology, Belgium	Ph.D.	02/1990	Neurobiology
KU Leuven, Group Science & Technology, Belgium	PD fellow	09/1993	Neuroscience
KU Leuven, Group Biomedical Sciences, Belgium	PD fellow	09/1995	Cardiovascular sciences

A. Personal statement

As a group leader in the Vesalius Research Center (Flemish Interuniversity Institute for Biotechnology - VIB), I contributed to an extensive research program in vascular and neural development and cardiovascular and neurodegenerative disorders (in collaboration with Prof. P. Carmeliet). In 2008, I became full professor at the Biology Department of KU Leuven, and head of the Neural Circuit Development and Regeneration (NCDR) research group, which has a strong interest in defining cellular/molecular mechanisms underlying neurodegeneration, neuroinflammation and regeneration in the injured, diseased or aged central nervous system (CNS) (http://bio.kuleuven.be/df/LM/). Within our research, we position the eye as the visual part of the brain, allowing preclinical research into pathological processes contributing to human neurodegenerative diseases. Over time, my team implemented several models for neurodegenerative and inflammatory eye diseases, and established injury paradigms in the optic nerve of both rodents and teleost fish, that allow studying neuronal/axonal regeneration in the CNS. We follow a multidisciplinary approach in which advanced *in vivo* ocular imaging technologies and visual function tests are being combined with detailed morphological phenotyping, using confocal/multiphoton/light-sheet microscopy, optical clearing and time-lapse imaging, and longitudinal and post-mortem morphometrical analyses to follow inflammatory and de/regenerative processes. Besides, *ex vivo*/*in vitro* retinal tissue/cell cultures, state-of-the-art opto- & chemogenetic, cell sorting and (single-cell) omics approaches are available to further study the cellular and molecular pathways underlying neuroprotection/regeneration. My profound experience with research in the field of CNS degeneration, and my particular expertise in morphological, functional and behavioral phenotyping of animal disease models for optic neuropathies/retinopathies are fundamental to the proposed project.

B. Positions and honors

Positions and employment

1990-1993	PD fellow, National Foundation for Scientific Research Belgium (NFWO), Laboratory of Neuroendocrinology & Immunological Biotechnology, KU Leuven, Belgium
1993-1995	PD fellow/Staff Scientist, Center for Molecular and Vascular Biology, KU Leuven, Belgium
1995-2007	Group Leader/Senior Scientist, Center for Transgene Technology and Gene Therapy, Flemish Interuniversity Institute for Biotechnology (VIB), Belgium
2000-2004	Assistant Professor, Faculty of Medicine, Department of Molecular Medicine, KU Leuven
2004-2007	Associate Professor, Faculty of Medicine, Department of Molecular Medicine, KU Leuven
2007-2008	Associate Professor, Faculty of Science, Department of Biology, KU Leuven, Belgium
2007-	Head of Neural Circuit Development and Regeneration RG, KU Leuven, Belgium
2008-	Full Professor, Faculty of Science, Department of Biology, KU Leuven, Belgium
2018-	Head of the Division of Animal Physiology and Neurobiology (11 PIs)
2018-	Board member of Department of Biology & member of the Advisory Board (BeCo) concerning hiring new Professors at the Faculty of Sciences, KU Leuven

Professional experiences and memberships

Reviewing and consulting activities

- Solicited reviewer for various journals, including Journal of Neuroscience, The Journal of Clinical Investigation, Journal of Cellular & Molecular Medicine, Faseb Journal, Investigative Ophthalmology and Visual Science, Experimental Eye Research, BMC Ophthalmology, Neural Regeneration Research.

- *Ad hoc* advisor 'in vivo preclinical research' at Oxurion NV, Belgium (2009-2019); consultant 'animal modeling/histology' at the Vesalius Research Center, VIB, Belgium (2010-2016); reviewer *ad hoc* for fellowships and R&D projects at the 'Agentschap Innoveren en Ondernemen' (VLAIO, previous IWT), Belgium (since 2006)
- Member of the Research Council KU Leuven (2005-2016); member of expert panel 'Functional Biology' at the Research Foundation Flanders (since 2010, panel-chair 2014-2016); member of the European Research Council (ERC) evaluation panel LS7 - Diagnostic tools, therapies and public health (since 2010, panel vice-chair 2012-2018), member of the Raad Internationale SamenwerkingsProjecten (RISP) KU Leuven (2020-)

Memberships

- Society for Neuroscience (SfN) - Federation of European Neurosciences (FENS) - International Society for Fibrinolysis & Proteolysis - Belgian Society for Cell and Developmental Biology - European Association for Vision & Eye Research (EVER) - Association for Research in Vision & Ophthalmology (ARVO)

Honors and Awards

- 1st Prize Fund for Research in Ophthalmology 2011, 2013, 2014, 2017 (promoter of PhD laureates Lies De Groef, Jessie van Houcke, Kim Lemmens & Jurgen Sergeys)

***Invited lectures and co-organizer* of scientific meetings**

- On average two to three per year, e.g. Gordon Conference on Matrix Metalloproteinases, May 19-24, 2013, Lucca, Italy; Workshop series "Current Trends in Biomedicine 2014": Proteases at work, October 20-22, 2014, Baeza, Spain; ARVO Optic Nerve Meeting 2015, December 8-11, 2015, Obergurgl, Austria; 4th European Zebrafish Principal Investigator meeting, March 15-19, 2016, Lisbon, Portugal; EVER meeting, September 27-30, 2017, Nice, France; 5th European Zebrafish Principal Investigator meeting, March 23-26, 2018, Trento, Italy; ARVO Optic Nerve Meeting 2018, December 13-14, 2018, Obergurgl, Austria; EVER meeting, October, 17-19, 2019, Nice, France; Fox Center for Vision Restoration (virtual) Workshop, October 19, 2020, Pittsburgh, US.
- Co-organizer of scientific meetings, e.g. the 28th Conference of European Comparative Endocrinologists, CECE, Aug 21-25, 2016, Leuven and 'Key role of the immune system in CNS regeneration', fTALES, May 10-11, 2021, Hasselt.

Valorization activities and patent applications (published and issued)

Performance of 'technology-transfer' or 'contract research' projects for industrial partners (industrial collaborations), i.e., initiating contacts, supervising experimental performance and project reporting. Over the years such projects were performed in collaboration with TiGenix NV, Solvay Pharmaceuticals, Neuronova, J&J PRD, Pfizer, Bioinvent, Oxurion NV, Amakem NV, pH Pharma Inc, and Bayer AG, among others.

- *Application Nr: 03704573.9-2402*-EP030 1229 – *A novel target to inhibit angiogenesis, Inventor(s): Carmeliet P., Collen D., Moons, L.; Assignee(s): VIB*
- Application Nr: EP 14 169 969 – *MMP-9 for enzymatic posterior vitreous detachment, Inventors(s): B. Jonckx, T.T. Hu, L. Arckens, L. Moons; Assignee(s): ThromboGenics NC, KU Leuven*

Scholastic experiences

- I have trained more than 20 junior laboratory technicians, over 90 MSc students, about 40 Belgian/foreign PhD students and 20 post-doc fellows, some of which currently have high-profile academic positions as independent group leaders at prestigious research institutions, e.g., Cardiology Department, Maastricht University (S. Heymans); International Center for Genetic Engineering and Biotechnology in Trieste (S. Zacchigna). I am currently mentoring/supervising 11 PhD students and 3 post-doc fellows.
- Since 2007 I teach Biology and Animal Physiology courses to bachelor and master students of Biology, Biochemistry & Biotechnology, Biomedical Sciences, and Bioengineering at KU Leuven, Belgium.

C. Contribution to Science (see ORCID: 0000-0003-0186-1411)

My scientific output consists of > 210 research papers in peer-reviewed international journals. This work resulted in a h-index of 65 and a total number of citations of 23366 (WoS, November 2020). A complete publication list can be found at: *https://lirias.kuleuven.be/cv?u=U0012643*.

I. As a junior scientist, I contributed as a key investigator to a landmark paper in the angiogenesis field, which described for the first time the generation and phenotyping of a mouse deficient for an angiogenic growth factor (studies led by Prof. P. Carmeliet, Angiogenesis and Vascular Metabolism RG, Department of Oncology). Mice that lack the VEGF gene on one allele, die early during embryonic development because of abnormal blood vessel formation, which highlights

a strict dose-dependent regulation of embryonic angiogenesis by this growth factor. This publication, which has been cited more than 5,800 times, formed the start of research related to VEGF (now more than 81,000 references on PubMed). VEGF still seems the 'prima dona' angiogenic factor and plays an important role in all processes and diseases characterized by insufficient or excessive angiogenesis. Numerous follow-up researches investigated the therapeutic potential of VEGF in ischemic tissue diseases and the use of neutralizing antibodies to VEGF to combat cancer and other diseases characterized by abnormal angiogenesis. This resulted in 2004 in the FDA approvement of Bevacizumab for treatment of human cancers and this drug, as well as follow-up compounds, are nowadays also heavily used in ophthalmological practice. PlGF is a homolog of VEGF, discovered only one year after VEGF, but its in vivo role in angiogenesis remained unknown for more than 10 years. In depth phenotyping of PlGF deficient mice, performed under my direct supervision, revealed, quite unexpectedly, that PlGF plays a specific key role during pathological angiogenesis but is not important for blood vessel formation during embryonic and postnatal development. Our research team further investigated the therapeutic potential of PlGF, as well as the interaction of PlGF and its receptor Flt-1, which resulted in many follow-up studies, and preclinical and clinical research investigating the therapeutic applications of PlGF neutralizing antibodies in cancer and ocular pathologies.

- *Carmeliet, P., et al. (1996). Abnormal blood vessel development and lethality in embryos lacking a single VEGF allele. Nature, 380 (6573), 435-9. PMID: 8602241*
- *Carmeliet, P., et al. (1999). Impaired myocardial angiogenesis and ischemic cardiomyopathy in mice lacking the vascular endothelial growth factor isoforms VEGF164 and VEGF188. Nature Medicine, 5 (5), 495-502. PMID: 10229225*
- *Carmeliet, P., et al. (2001). Synergism between vascular endothelial growth factor and placental growth factor contributes to angiogenesis and plasma extravasation in pathological conditions. Nature medicine, 7 (5), 575-583. PMID: 11329059*
- *Luttun, A., et al. (2002). Revascularization of ischemic tissues by PlGF treatment, and inhibition of tumor angiogenesis, arthritis and atherosclerosis by anti-Flt1. Nature medicine, 8 (8), 831-40. PMID: 12091877*

II. Within an intense collaboration with Prof. I. Stalmans (Ophthalmology RG, Department of Neurosciences, KU Leuven), my group, established at the Biology Department of KU Leuven in 2007, further investigated the involvement of VEGF and PlGF, as well as other important players (e.g. Rho-kinases) in angiogenic, fibrotic and neuroinflammatory processes in glaucoma and other prevalent retinopathies. These studies resulted in several important papers showing a clear potential of combinatorial VEGF and PlGF inhibition in reducing pathological angiogenesis, inflammation and fibrosis. It also resulted in fruitful collaborations with industrial partners in Flanders, developing new therapeutic compounds for a number of important ocular diseases (e.g. Oxurion NV, Heverlee & Amakem NV, Diepenbeek; Belgium). Furthermore, based on these studies I was granted, together with Profs. L. Arckens (Neuroplasticity and Neuroproteomics RG, Department of Biology) and I. Stalmans, two prestigious Hercules awards (2010 & 2014), which enabled the founding of the **'Vision Core Leuven' (VCL)**, a preclinical service platform comprising state-of-the-art technology to study ocular pathologies at morphological and functional level, that allows the identification of novel targets and drug testing in ocular diseases and beyond (see: http://www.visioncore.be/). The VCL currently runs projects with industrial partners (e.g. Bayer AG, pH Pharma Inc) on a fee-for-service basis.

- *Li, Z., et al. (2009). Inhibition of Vascular Endothelial Growth Factor Reduces Scar Formation after Glaucoma Filtration Surgery. Investigative Ophthalmology & Visual Science, 50 (11), 5217-5225. PMID: 19474408*
- *Van Bergen, T., et al. (2013). Inhibition of placental growth factor improves surgical outcome of glaucoma surgery. Journal of Cellular and Molecular Medicine, 17 (12), 1632-1643. PMID: 24118824*
- *Hollanders, K., et al (2015). The effect of AMA0428, a novel and potent ROCK inhibitor, in a model of neovascular age-related macular degeneration. Investigative Ophthalmology & Visual Science, 56(2):1335-48. PMID: 25626969*
- *Van Bergen, T., et al. (2018). The role of placental growth factor (PlGF) and its receptor system in retinal vascular diseases. Progress in Retinal and Eye Research, 69:116-136. PMID: 30385175*

III. WIthin a landmark study, to which I contributed as the leading PI, we showed for the first time the involvement of VEGF in adult-onset progressive motor neuron degeneration reminiscent of amyotrophic lateral sclerosis (ALS). Besides disclosing that reduced VEGF expression increases the risk for ALS in humans, we showed that intracerebroventricular administration of VEGF to rats with ALS improved disease progression and survival time. Together with other preclinical validation studies, this resulted in clinical trials envisioning the therapeutic use of VEGF for treatment of ALS. These studies instigated my interest in neurodegenerative diseases and led me to further studying the molecules and mechanisms contributing to the degenerative phenotype in glaucoma. Besides investigating the role of MMPs in retinal ganglion cell (RGC) degeneration using various rodent glaucoma models, we developed a keen interest in studying the involvement of the brain in this blinding disease, which resulted in a paper that revealed a clear neuroprotective effect

of chronic brain target stimulation in the glaucomatous retina. These studies also ensued a new direction towards investigating the eye phenotype in Parkinson's and Alzheimer disease. Here, our primary goal is to **develop better treatments for degenerative disorders that target the eye and the brain**. As such, my team recently initiated researches into the degenerative phenotype in Wolfram syndrome, a rare childhood disease characterized by, amongst other pathologies, retina and brain degeneration. This again highlights my focus on eye-brain connections in neurodegenerative pathologies.

- *Oosthuyse, B., et al. (2001). Deletion of the hypoxia-response element in the vascular endothelial growth factor promoter causes motor neuron degeneration. Nature Genetics, 28 (2), 131-138. PMID: 11381259*
- *Storkebaum, E., et al. (2005). Treatment of motoneuron degeneration by intracerebroventricular delivery of VEGF in a rat model of ALS. Nature Neuroscience, 8 (1), 85-92. PMID: 15568021*
- *De Groef, L., et al. (2014). MMPs in the neuroretina and optic nerve: modulators of glaucoma pathogenesis and repair?. Investigative Ophthalmology & Visual Science, 55 (3), 1953-1964. PMID: 24681977*
- *Geeraerts E., et al. (2019). Optogenetic stimulation of the superior colliculus confers retinal protection in a mouse glaucoma model. Journal of Neuroscience 39 (12), 2313-2325. PMID: 30655352*
- *Claes, M., et al. (2019). Target-Derived Neurotrophic Factor Deprivation Puts Retinal Ganglion Cells on Death Row: Cold Hard Evidence and Caveats. International Journal of Molecular Sciences, 20 (17): 4314-. PMID: 31484425*

IV. My lab also focuses on studying axonal regeneration within the retinofugal system, with a specific interest in the role of neuroinflammation in fueling optic nerve regrowth. Within this regenerative research, we employ our unique expertise in contrasting spontaneously regenerating teleost fish and non-regenerating mammals to investigate the underlying mechanisms of injury-induced axonal repair and functional circuit recovery. The ongoing research focuses on defining the intercellular molecular crosstalk between retinal neurons, microglia/macrophages and macroglia. Furthermore, recent in-house generated data provide pioneering evidence that dendritic shrinkage is an important driver of axonal regrowth in damaged neurons, and suggest that intraneuronal energy redistribution drives the spontaneous regeneration and functional recovery in the zebrafish optic nerve. Based on the hypothesis that differential mitochondrial dynamics and an altered cellular energy metabolism in the neuronal compartments underlie this 'dendrites for regeneration' paradigm we are currently identifying the intra-neuronal bioenergetics contributing to successful injury-induced neural circuit repair.

- *Lemmens, K., et al. (2016). Complementary research in mammals and fish indicates MMP-2 as a pleiotropic contributor to optic nerve regeneration. Neural Regeneration Research, 11 (5), 740-742. PMID: 29189905*
- *Bollaerts, I., et al. (2017). Neuroinflammation as Fuel for Axonal Regeneration in the Injured Vertebrate Central Nervous System. Med Inflamm, 2017: 10.1155/2017/9478542. PMID: 28203046*
- *Beckers A., et al. (2019). An Antagonistic Axon-Dendrite Interplay Enables Efficient Neuronal Repair in the Adult Zebrafish Central Nervous System. Molecular Neurobiology, 56 (5), 3175-3192.*
- *Lefevere E., et al. (2020). Tightening the retinal glia limitans attenuates neuroinflammation after optic nerve injury. Glia, 68(12):2643-2660. PMID: 32645232*

V. As a growing number of elderly in our aging society is suffering from age-associated neurodegenerative diseases, I decided to add a high-priority goal to my research: define the cellular and molecular aspects of physiological and pathological CNS ageing and investigate the impact of ageing on the restoration capacity of the CNS. My first work using spontaneously regenerating zebrafish, identified a clear impact of aging on the axonal regrowth potential and identified both neuronal intrinsic and extrinsic mechanisms, e.g. inflammaging, as underlying processes. In 2016, I invested in setting up an innovative research consortium around the upcoming gerontology model, *Nothobranchius furzeri or killifish, and established, t*ogether with profs. L. Arckens and E. Seuntjens, a breeding and husbandry facility to support killifish physiology research. I secured project and fellowship fundig that allowed me to already define the specific ageing hallmarks in the klillifish retina and brain, and how aging impacts on its neuronal and axonal regenerative potential. The results of those studies are being prepared for two publications. Preliminary evidence, generated in house, revealed the presence of Aβ plaques and tauopathy in old killifish, and these signs of spontaneous neurodegeneration in aged fish urge to further investigate the onset and pathogenesis of the degenerative phenotype. All in all, our recent investigations revealed that the killifish constitutes a promising model organism for investigating ageing biology and its impact on CNS repair, and might inspire new strategies for brain rejuvenation and healthy aging.

- *Van houcke, J., et al. (2015). The zebrafish as a gerontology model in nervous system aging, disease, and repair. Ageing Research Reviews, 24(Pt B):358-68 358-368. PMID: 26538520*

- *Van Houcke J*., Bollaerts I*., et al. (2017). Successful optic nerve regeneration in the senescent zebrafish despite age-related decline of cell intrinsic and extrinsic response processes. Neurobiology of Aging, 60, 1-10. PMID: 28917662*
- *Van houcke, J., et al. (2019). Extensive growth is followed by neurodegenerative pathology in the continuously expanding adult zebrafish retina. Biogerontology, 20 (1), 109-125. PMID: 30382466*
- *Vanhunsel, S., et al. (2020). Designing neuroreparative strategies using aged regenerating animal models. Ageing Research Reviews, 62, Art.No. 101086. doi: 10.1016/j.arr.2020.101086. PMID: 32492480*

D. Research support (past 3 years)

Over the past decade I participated in many projects and grants, including EU grants, international research grants and national grants, both as promoter or co-promoter. A few most recent completed/ongoing applications:

Completed research support projects (ending 2015 or beyond)

- IWT SBO 110068 2011 - 2015 Role: co-PI
  "SBO-OPTOBRAIN - Innovative optogenetics for research and translational brain applications"
  Goal: Implement, optimize and develop optogenetics approaches for neuroscience research
- KU Leuven - OT14/00830 2015 - 2018 Role: PI
  "The yin and yang of neuroinflammation: in search for novel neuroprotective and regenerative molecules"
  Goal: Investigate whether acute inflammation contributes to RGC axonal regeneration: a proteomics approach
- FWO G0B2315N 2015 - 2018 Role: PI
  "Identification of neuroprotective/regenerative molecules: the importance of a balanced neuroinflammation"
  Goal: Investigate whether inflammaging contributes to RGC axonal regeneration in adult and aged zebrafish
- FWO Flanders-Quebec bilateral research grant 2016 - 2018 Role: PI
  "The interplay between dendrite & axon regeneration in central nervous system repair: which way to grow?"
  Goal: Investigate axon versus dendrite outgrowth in the injured retino-thalamic system
- AKUL/HER/13/09 Animal Vision Center 2014 - 2019 Role: PI
  Goal: Set up a platform, including a HRA, OCT, optomotor, Y maze, to investigate the anatomical and functional integrity of the visual system of zebrafish, mice, rats and rabbits.
- IOF-KU Leuven - C32/16/004 2017 - 2019 Role: PI
  "Vision Core Leuven': a service platform for compound screening and disease modeling in the eye"
  Goal: Establish a multidisciplinary service platform that offers a unique portfolio of relevant eye disease models, state-of-the-art technologies and functional readouts
- FWO G053217N 2017 - 2020 Role: PI
  "Neuroinflammation as fuel for axonal regeneration:exploring the proteome for underlying molecular players"
  Goal: Identifying the underlying molecules and pathways linking neuroinflammation to axonal regeneration

Ongoing research support

- AKUL/HER/17/011: FACsorting platform 2018 - 2023 Role: co-PI
  Goal: Establish a single cell(-type) platform for biological applications in diverse model organisms
- KU Leuven - C14/18/053 2018 – 2022 Role: PI
  "Intra-neuronal energy channeling: a prerequisite for functional CNS repair"
  Goal: Investigating the cellular metabolic processes driving axonal regeneration in the visual system
- Queen Elisabeth Medical Foundation 2020 – 2022 Role: PI
  "Oligodendrocytes in Wolfram syndrome: bystanders or partners in crime?"
  Goal: Study the differential contribution of neurons *versus* oligodendrocytes to Wolfram syndrome pathogenesis
- Central Europe Leuven Strategic Alliance (CELSA) 2020 – 2022 Role: PI
  "Ferroptosis: a novel paradigm in the neurodegenerative pathology of Wolfram syndrome"
  Goal: Study ferroptosis as a disease mechanism underlying the ocular phenotype in Wolfram syndrome
- EU Joint Programme - Neurodegenerative Disease Research 2021 – 2023 Role: partner
  "Global retinal imaging consortium for Alzheimer's disease (BRAINSTORM)"
  Goal: Preclinical and clinical research into retinal biomarkers for Alzheimer's diagnosis

PhD & PD Fellowships (2017-2020)

Over the past 3 years I secured national (academic and industrial) funding for 8 PhD and 4 post-doc fellowships.