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[Giulia Lunghi]
CURRICULUM VITAE

INFORMAZIONI PERSONALI (NON INSERIRE INDIRIZZO PRIVATO E TELEFONO FISSO O CELLULARE)

COGNOME	**LUNGHI**
NOME	**GIULIA**
DATA DI NASCITA	07/01/1994

TITOLI

TITOLO DI STUDIO

2015-2017
Master Degree in Medical Biotechnology and Molecular Medicine
Department of Medical Biotechnology and Translational Medicine, University of Milano
Thesis Title: "Sviluppo di modelli neuronali *in vitro* caratterizzati da accumulo di glucosilceramide per lo studio della malattia di Parkinson e della malattia di Gaucher"
Grade: 110/110 *cum laude*
Supervisor: Massimo Aureli, Professor

2012-2015
Bachelor's Degree in Medical Biotechnology
Department of Medical Biotechnology and Translational Medicine, University of Milano
Grade: 110/110 *cum laude*
Thesis Title: "Accumulo lisosomiale di sfingomielina in fibroblasti da pazienti affetti da malattia di Niemann-Pick: valutazione del suo effetto sull'alterazione dei meccanismi legati all'autofagia"
Supervisor: Massimo Aureli, Professor

TITOLO DI DOTTORE DI RICERCA O EQUIVALENTI, OVVERO, PER I SETTORI INTERESSATI, DEL DIPLOMA DI SPECIALIZZAZIONE MEDICA O EQUIVALENTE, CONSEGUITO IN ITALIA O ALL'ESTERO

2017-2020
PhD student in Biochemical sciences (Thesis Defence: December 9th, 2020)
Department of Medical Biotechnology and Translational Medicine, University of Milano
Thesis Title: "GM1 oligosaccharide modulation of calcium signalling in neuronal functions"
Supervisors: Sandro Sonnino, Professor and Elena Chiricozzi, Professor

CONTRATTI DI RICERCA, ASSEGNI DI RICERCA O EQUIVALENTI

2022-now
Type A Postdoctoral Fellow

Department of Medical Biotechnology and Translational Medicine (BioMeTra Dep.), University of Milano
Supervisor: Massimo Aureli, Professor

2020-2022
Type B Postdoctoral Fellow
Department of Medical Biotechnology and Translational Medicine, University of Milano
Supervisor: Massimo Aureli, Professor

ATTIVITÀ DIDATTICA A LIVELLO UNIVERSITARIO IN ITALIA O ALL'ESTERO

Academic year 2023/2024 – 12 hours
Professor on contract of the Biochemistry course (SSD BIO/10), International Medical School, University of Milano

Academic year 2023/2024 – 10 hours
Professor of the "Analysis of lipid content in cellular models" course (SSD BIO/10), Doctoral education, PhD program in Translational Medicine, University of Milano

Academic year 2022/2023 – 2 hours
Professor of the Biochemistry module (SSD BIO/10), Course of Basic Sciences, Nursery Bsc program, Medical School, University of Milano (in quality of Biochemistry expert, course hold by Prof. Elena Chiricozzi)

Academic year 2022/2023 – 6 hours
Assistant of the Biochemistry course (SSD BIO/10), Degree of International Medical School, University of Milano

Academic years 2018/2019, 2019/2020, 2020/2021, 2021/2022, 2022/2023- 48 hours/year
Assistant for laboratory training of Cellular and Molecular Methodologies Course, Bachelor's Degree of Medical Biotechnology, University of Milano

Academic years 2017/2018; 2018/2019 – 48 hours/year
Assistant for laboratory training of the Human Biochemistry Course, Master's Degree of Medical Biotechnology and Molecular Medicine, University of Milano

Academic year 2018/2019- 29 hours
Assistant for laboratory training of the Biochemistry Course, Degree of International Medical School, University of Milano

SUPERVISIONE DI TESI

Academic year 2020/2021
Co-supervisor in the Master's degree thesis of Laura Cioccarelli (Matr. 953844)
Master degree in Medical Biotechnology and Molecular Medicine, University of Milano
Title: "Glucosylceramide accumulation in the onset of neuronal damage: study of the molecular mechanism and of a potential therapeutic approach in hiPSCs-derived dopaminergic neurons"

Academic year 2021/2022
Co-supervisor in the Master's degree thesis of Elena Catalani (Matr. 980310)
Master degree in Medical Biotechnology and Molecular Medicine, University of Milano
Title: "Study of the role of β-Glucocerebrosidase deficiency in the onset of neurodegeneration in hiPSCs-derived dopaminergic neurons"

Academic year 2021/2022
Co-supervisor in the Bachelor's degree thesis of Laura Vigani (Matr. 975972)
Bachelor degree in Medical Biotechnology, University of Milano
Title: "Studio degli effetti della doppia mutazione N370S/F213I del gene GBA sul differenziamento neuronale di iPSCs umane"

DOCUMENTATA ATTIVITÀ DI FORMAZIONE O DI RICERCA PRESSO QUALIFICATI ISTITUTI ITALIANI O STRANIERI

October 2020-present

BioMeTra Department, University of Milano, Italy (Postdoc)

My research activity is currently focused on the involvement of the sphingolipids in the regulation of the cell homeostasis and their implication in several pathologies, with a specific focus on neurodegeneration.
Specifically, I am working on two projects: i) from one side I am defining the molecular mechanisms linking β-glucocerebrosidase loss of function with the neurodegeneration occurring in Gaucher disease and in GBA-dependent Parkinson's disease, ii) from the other side, I am investigating the molecular mechanism linking GM1 ganglioside deficiency to sporadic Parkinson's disease (sPD).

i) β-glucocerebrosidase (GCase) is a lysosomal glycohydrolase encoded by the GBA gene, responsible for the catabolism of the sphingolipid glucosylceramide (GlcCer). Deficiency of this enzyme is responsible for the lysosomal accumulation of GlcCer, leading to the onset of GCase-related pathologies that are characterized by neurodegeneration and comprise Gaucher Disease (GD) and GBA-dependent Parkinson's disease (GBA-PD). This project consists in the evaluation of the molecular mechanisms at the basis of neurodegeneration occurring in GD and in GBA-PD. To investigate this linkage, I developed an *in vitro* model of the neuronal form of GD represented by induced Pluripotent Stem Cells (iPSCs)-derived dopaminergic neurons, obtained from healthy subjects, treated with CBE, a specific inhibitor of β-glucocerebrosidase (GCase). I found that CBE-treated neurons present a progressive and time-dependent accumulation of glucosylceramide (GlcCer) at the lysosomal level. Moreover, CBE-treated neurons showed a neurodegenerative phenotype and an increased lysosomal biogenesis and exocytosis, the latter responsible for a modification of the lipid and protein composition of the plasma membrane that could leads to the neuronal damage (**Lunghi *et al* 2021 *Cells***). Moreover, considering the central role of lysosomes in the recycling of metabolites, I'm investigating the effect of the lysosomal impairment, due to glucosylceramide accumulation, on the metabolic flow through targeted metabolomics analysis by mass spectrometry (LC-MS/MS). I found an alteration in the glucose metabolism, with a slow-down of both the glycolytic pathway and Krebs cycle, and an increase in the content of amino acids, used as alternative energy source. The use of dopaminergic neurons and midbrain organoids derived from iPSCs obtained from PD and GD-PD patients will be used to confirm the hypothesised molecular mechanism.

ii) Accumulating evidences is pointing out a central role for GM1 ganglioside in the onset of sPD. Indeed, the neuronal content of ganglioside GM1 progressively declines with aging, leading to neuropathological dysfunction in several brain key areas. Accordingly, the efficacy of GM1 replacement therapy has been shown for PD preclinical models, which however is largely lost in clinics due to GM1 amphiphilicity that limits the blood-brain barrier (BBB) passage. During my PhD, I demonstrated that the GM1 oligosaccharide (OligoGM1) can replace the GM1 neuronal function by directly interacting with TrkA receptor at the plasma membrane. Moreover, by proteomic and biochemical analysis, I revealed a broad spectrum of molecular events prompted by OligoGM1 in a Trk-dependent manner, involving calcium regulation, antioxidant mechanism, mitochondrial bioenergetics and anti-inflammatory response. Given the OligoGM1 properties, we are investigating its therapeutic potential. First, in collaboration with Artois University, I pointed out the OligoGM1 ability to cross the BBB with a rate 20-fold higher than GM1 and by a time-concentration dependent paracellular way **(Lunghi *et al* 2020 *IJMS*)**. The OligoGM1 effect was first evaluated in MPTP *in vitro* and *in vivo* models of sPD **(Lunghi *et al* 2023 *Biomedicines)*** and then in the heterozygous *B4GalNAcT1*$^{+/-}$ mouse, a physiological *in vivo* model of sporadic PD, in collaboration with Rutgers University. Here we demonstrated that OligoGM1 systemically administered to these mice was able to completely rescue the motor symptoms, reduce nigral alpha-synuclein aggregates, recovery the nigral dopaminergic neurons and to restore the striatal neurotransmitters level. Importantly, this study highlighted the therapeutic potential of the OligoGM1 for the treatment of sporadic PD **(Chiricozzi, Lunghi *et al* 2019 *Scientific Reports*).** Actually, to specifically detail how OligoGM1 is able to counteract the alpha-synuclein (αS) toxicity, I analysed the OligoGM1 ability to inhibit αS aggregation *in vitro* in collaboration with UCL, UK. In particular, by the real-time quaking-induced conversion (RT-QuIC)-assay, I demonstrated that OligoGM1 is sufficient to suppress the spontaneous αS aggregation and the one induced by exposure to preformed αS fibrils. In parallel, I showed the OligoGM1 capability to protect DA-neurons co-cultured with microglia from αS toxicity by reducing the neuronal loss, increasing the dendrite network and by reducing the microglia activation **(Fazzari, Lunghi *et al.* BBA 2023)**. I am actually translating the obtained data by exploiting the use of human DA-neurons and midbrain organoids derived from iPSCs obtained from fibroblasts of a healthy subject treated with preformed αS fibrils and of PD patients, to evaluate the ability of OligoGM1 to modulate αS aggregation and the related molecular mechanism. The final proof of concept is to study the

potential of OligoGM1 in blocking αS aggregates induced toxicity and subsequent inflammation *in vivo*. To prove that, I worked as visiting scientist in the laboratory of Professor Vekrellis at BRFAA Greece, which recently developed a well-established αS mouse model.

September 2023–December 2023
Biomedical Research Foundation of the Academy of Athens (BRFAA), Athens, Greece (visiting scientist)
Project: GM1 oligosaccharide efficacy against α-synuclein aggregation and toxicity in vivo
The purpose of this project is to expand the current knowledge by shedding new light on OligoGM1 protective activity against αS aggregation *in vivo*. Specifically, OligoGM1 capability to protect from αS aggregation and to modulate inflammation, and through which molecular mechanism this occurs, are being addressed in WT mice (C57Bl6) intrastriatally injected with human αS pre-formed fibrils and daily IP injected with OligoGM1 for 28 days. Specifically, the objectives of this project are *i)* to evaluate the effect of OligoGM1 on α-syn aggregation; *ii)* to evaluate the effect of OligoGM1 on neuronal inflammation; *iii)* Identification of OligoGM1 modulated pathways. These findings will permit to understand the OligoGM1 potential against the αS fibrillation, a key event in PD, thus providing a strong support for moving the OligoGM1 as a drug candidate for PD. I have performed these experiments in the laboratory of Prof. Vekrellis at the Division of Basic Neurosciences at the Biomedical Research Foundation of the Academy of Athens (BRFAA), thanks to their expertise in this field. The analysis of the results are ongoing.

October 2017-September 2020
BioMeTra Department, University of Milano, Italy (PhD student)
During my PhD in biochemical sciences at the department of Medical Biotechnology and Translational Medicine at the University of Milano, I started to study the molecular basis underling the neurotrophic and neuroprotective properties of the ganglioside GM1 using different *in vitro* and *in vivo* experimental models. Several data suggest a specific role of ganglioside GM1 in neuronal differentiation and neuronal protection, but the molecular mechanisms behind these processes are largely unknown. Together with my team, I demonstrated that only the GM1 oligosaccharide, rather than the ceramide portion, was directly involved in these processes. Specifically, we proved that the specific sugar chain of GM1 (GM1 oligosaccharide, OligoGM1) can replace the GM1 ganglioside function in relation to neuronal differentiation and protection by directly interacting with NGF specific receptor TrkA at the plasma membrane level, leading to the activation of ERK1/2 downstream pathway **(Chiricozzi, Lunghi *et al* 2019 *Mol Neurobiol*; Di Biase, Lunghi *et al* 2020 *Glyoconj J*).** Moreover, by proteomic and biochemical analysis, we revealed a broad spectrum of molecular events prompted by OligoGM1 in a Trk-dependent manner, involving Ca^{2+} regulation, antioxidant mechanisms, mitochondrial bioenergetics **(Fazzari, Lunghi *et al* 2020 *Glyoconj J*)**, and anti-inflammatory response. In particular, I observed, by calcium imaging, that OligoGM1 administration to undifferentiated neuroblastoma Neuro2a cells resulted in an increased calcium influx, mediated by the activation of TrkA receptor. The results suggest that GM1 oligosaccharide is responsible for the regulation of calcium signaling at the base of the neuronal functions mediated by ganglioside GM1 **(Lunghi *et al* 2020 *Glycoconj J*)**.

November 2016-October 2017
BioMeTra Department, University of Milano, Italy (Msc Student)
During my master internship, my research activity has been focused on Gaucher disease (GD), a lysosomal storage disorder, caused by mutations in GBA1 gene coding for the lysosomal enzyme β-glucocerebrosidase (GCase). GCase is responsible for the degradation of glucosylceramide (GlcCer) and its deficiency determines the lysosomal accumulation of the GlcCer. Notably, the most severe form of GD is characterized by the impairment of the central nervous system, leading to neurodegeneration. To date, the most common genetic risk factor for Parkinson's Disease (PD) is represented by GBA1 mutations. Recently a possible connection between GD and PD has been suggested, although the molecular link between the two diseases is still obscure. With the aim to investigate the possible role of GBA1 deficiency and the consequent lysosomal GlcCer accumulation in the onset of neurodegeneration, I used an *in vitro* model suitable for the study of PD-GBA disease represented murine granule neurons treated with conduritol-B-epoxide (CBE), in order to pharmacologically inhibit the enzyme β-glucocerebrosidase GBA1. CBE-treated cells showed a progressive time-dependent GlcCer accumulation as well as an augmented content of its deacetylated and toxic form glucosylsphingosine. Moreover, I pointed out an increased lysosomal biogenesis, autophagy block and synaptic degeneration. These results suggest CBE-treated neurons as a new promising *in vitro* model of GlcCer accumulation, useful to investigate the possible correlation of lysosomal impairment in the molecular mechanisms underlying PD-GBA. Moreover, in human fibroblasts loaded with sucrose as a model of lysosomal accumulation, me and my team demonstrated the existence of a lysosome–plasma membrane–sphingolipid axis that could link the lysosomal storage to the cell growth arrest **(Samarani, Lunghi *et al* 2018 *FASEB J*).**

March 2015-July 2015

BioMeTra Department, University of Milano, Italy (Bsc Student)

My research activity has been started on the study of Niemann Pick Disease, a sphingolipidosis characterized by an accumulation of sphingomyelin (SM) in lysosomes, due to the deficiency of acid sphingomyelinase. To study the correlation between this accumulation and the onset of lysosomal dysfunction, I used fibroblasts derived from Niemann-Pick type A patients. In particular, I focused my attention on the effect of SM accumulation on the expression of the transcription factor EB (TFEB), a master regulator of lysosomal functions and the related autophagy. I found that the SM accumulation induced a nuclear translocation of TFEB, followed by an increased lysosomal biogenesis and by a deregulation of autophagy processes. Moreover, I showed an increased expression of the main acid glycohydrolases with the consequent alteration of lipid metabolism due to the lysosomal impairment in Niemann-Pick fibroblasts **(Carsana, Lunghi *et al*. 2022 *Journal of Molecular Neuroscience*).**

COLLABORATIONS

The research activity described above is implemented in the context of national and international collaborations that allowed me to obtain a good degree of independence and large capability of discussion:

- Professor Nico Mitro, Milano University, Milano, Italy
- Professor Claudio Fenizia, Milano University, Milano, Italy
- Professor Ivano Eberini, Milano University, Milano Italy
- Professor Kostas Vekrellis, BRFAA, Athens, Greece
- Dr. Tim Bartles, London College University, London, UK
- Neurosys CNS/PNS service, 410 Chemin Dep, Gardanne, France
- Professor Fabien Gosselet, Artois University, Lens, Lille, France
- Dr. Michela Deleidi, Institute Imagine, Paris, France
- Dr. Alessio di Fonzo, Policlinico Hospital of Milan, Italy
- Dr. Michael Speeding, Speeding Research Solution, France
- Professor Robert Ledeen, Rutgers University, Newark, NJ, US

September 2019

Introductory course in animal experimentation

University of Milano

November 2018

XL ALEMBIC Theoretical and Practical Course of Optical and Electron Microscopy

Advanced Light and Electron Microscopy Center (ALEMBIC), IRCCS San Raffaele Hospital, Milano, Italy

June 2018

Research Integrity - Natural and Physical Sciences course

October 26-27, 2017

PhD course "Signal pathways and their relevance for human pathology"

LITA (Laboratorio interdisciplinare di tecnologie avanzate), Segrate (MI)

CAPACITÀ E COMPETENZE TECNICHE

TECHNICAL SKILLS: during my scientific training I acquired a great experience in the field of biochemistry and molecular/cellular biology and, in particular, in the following methodologies: (i) **Biochemistry:** SDS-PAGE and Western Blotting, determination of enzyme activities with natural, florigenic and radiolabelled substrates, tissue and cell lipid analysis, DRM preparation; protein immunoprecipitation; (ii) **Cell biology:** maintenance and manipulation of cell cultures including primary neurons cultures, human blood-brain barrier cells, induced pluripotent stem cells cultures, differentiation of induced pluripotent stem cells into dopaminergic neurons, differentiation of induced pluripotent stem cells into midbrain organoids, Extracellular Vescicles (EVs) isolation; (iii) **Molecular biology:** DNA/RNA extraction, primers design, PCR, qPCR, bacterial transformation; (iv) **Imaging experiments:** Immunohistochemistry (IHC) and Immunocytochemistry (ICC) with qualitative

and quantitative analysis by wide-field microscopy; calcium imaging (v) ***In vivo*****:** mice manipulation (C57BL/6 and CD1 strains), behavioral analysis, drug intraperitoneal injection, stereotaxic striatal injections, sacrifice via perfusion or cervical dislocation, brain dissection, isolation of different organs, preparation of cerebellar granule neurons from P5 C57BL/6.

INFORMATIC SKILLS: excellent knowledge of Word, Excel, Power Point (Microsoft Office), statistical analysis software (Prism), image analysis software (ImageJ).

LANGUAGES:
- Italian (native)
- English (B2, FCE certificate)

PROGETTI DI RICERCA FINANZIATI

Role: Principal Investigator
Funding Agency: European Molecular Biology Organization - EMBO Scientific Exchange Grant 10222
Title: "GM1 oligosaccharide efficacy against α-synuclein aggregation and toxicity in vivo"
Amount of Money Allocated: EUR 6300
Description: The purpose of this project is to expand the current knowledge by shedding new light on OligoGM1 protective activity against αS aggregation *in vivo* by using WT mice (C57Bl6) intrastriatally injected with human αS pre-formed fibrils and daily IP injected with OligoGM1 for 28 days.

Role: Principal Investigator
Funding Agency: International Society for Neurochemistry - ISN International Travel Support March 2023
Title: "GM1 oligosaccharide efficacy against α-synuclein aggregation and toxicity in vivo"
Funding: USD 4000
Description: The purpose of this project is to expand the current knowledge by shedding new light on OligoGM1 protective activity against αS aggregation *in vivo* by using WT mice (C57Bl6) intrastriatally injected with human αS pre-formed fibrils and daily IP injected with OligoGM1 for 28 days.

Role: Principal Investigator
Funding Agency: BraYn association - BraYn Trainee Travel Grant "Placido Illiano" 2023
Title: "GM1 oligosaccharide efficacy against α-synuclein aggregation and toxicity in vivo"
Funding: EUR 500
Description: The purpose of this project is to expand the current knowledge by shedding new light on OligoGM1 protective activity against αS aggregation *in vivo* by using WT mice (C57Bl6) intrastriatally injected with human αS pre-formed fibrils and daily IP injected with OligoGM1 for 28 days.

Role: CO-Principal Investigator
Funding Agency: Milano University, Seed4Innovation program – 2021/2022
UGOV: UGOV SEED4I_2021_04
Title: "Oligosaccharides for the treatment of Parkinson's Disease: bacterial synthesis of GM1 oligosaccharide–OLIGOtoGO"
Amount of Money Allocated: EUR 50000
Description: This research project is aimed to develop a new procedure for GM1 oligosaccharide bacterial production.

Role: CO-Principal Investigator
Funding Agency: Italian Ministry of Economic Development, Seed4Innovation_PoCe_MISE program – 2021/2022
UGOV: TT_MIN21_SEED4IP_03
Title: "GM1 oligosaccharide: the new therapeutic drug for sporadic Parkinson's Disease"
Amount of Money Allocated: EUR 40000
Description: This research project is aimed at analyzing in detail the behaviour of the GM1 oligosaccharide (OligoGM1) once administered to a complex living organism. Specifically, we will test different doses and routes of administration in order to study OligoGM1 pharmacokinetics.

RGANIZZAZIONE, DIREZIONE E COORDINAMENTO DI GRUPPI DI RICERCA NAZIONALI E INTERNAZIONALI, O PARTECIPAZIONE AGLI STESSI

Role: Principal Investigator
Project: GM1 oligosaccharide efficacy against α-synuclein aggregation and toxicity in vitro and in vivo
Founding: EMBO Scientific Exchange Grant 10222, ISN travel support March 2023, and BraYn Trainee Travel Grant "Placido Illiano" 2023
Partners: Dr. Tim Bartles, UCl, London, UK and Prof Kostas Vekrellis, Division of Basic Neurosciences, BRFAA, Athens, Greece
Alpha-synuclein (αS) fibrillation and aggregation are considered crucial steps in PD pathophysiology and preventing its misfolding and/or promoting its clearance can represent the keystone for PD cure. In this scenario, GM1 ganglioside could represent the promising molecule able to directly interact with αS and inhibit its fibrillation, to promote its degradation via autophagy and finally avoid PD neurodegeneration. Unfortunately, the low GM1 capability to reach central nervous system (CNS) hampers its clinical use. However, our newly discovery that the oligosaccharide chain (OligoGM1) alone is able to faithfully replicate the ganglioside functions open new promising therapeutic perspective. Indeed, losing the amphiphilicity of the entire ganglioside, OligoGM1 efficiently cross the BBB via a passive paracellular route without being internalized and metabolized by cells, thus remaining active and capable to activate the Trk pathways. Such capability allowed its *in vivo* penetration in all brain regions and the complete recovery of a PD mouse model. In this setting, this project aims at understanding how OligoGM1 can protect from αS toxicity *in vitro*. Specifically the objectives of this proposal are *i)* to verify a direct OligoGM1:αS interaction preventing an αS amyloidogenic misfolding; *ii)* to analyse the molecular pathways modulated by OligoGM1 in presence of aggregated αS; *iii)* to address the involvement of glial cells and neuroinflammation due to aggregated αS.
In collaboration with Dr. Tim Bartels, at UK Dementia Research Institute at UCL, I analysed the OligoGM1 ability to inhibit αS aggregation *in vitro* ***(*Lunghi *et al.* 2023 *Biochim Biophys Acta Mol Cell Biol Lipids*)**. In particular, by RT-QuIC *in vitro* assay exploiting Thioflavin T dye fluorescence, we demonstrated that the presence of OligoGM1 is sufficient to suppress the spontaneous αS aggregation and the one induced by exposure to preformed αS fibrils.
Moreover, I tested the neuroprotective capability of OligoGM1 to protect from αS toxicity, by exposing rat dopaminergic neurons co-coltured with microglia to αS oligomers. By ICC analysis, OligoGM1 was found to counteract the neuronal loss and the dendrite network disruption caused by αS oligomers neurotoxicity. Additionally, OligOGM1 reduced microglia activation by lowering OX-41 signal, marker of pro-inflammatory (M1) active microglia ***(*Lunghi *et al.* 2023 *Biochim Biophys Acta Mol Cell Biol Lipids*)**.
In collaboration with Prof. Vekrellis at the Division of Basic Neurosciences at the Biomedical Research Foundation of the Academy of Athens (BRFAA), I'm evaluating the OligoGM1 protective activity against αS aggregation *in vivo*. Specifically, OligoGM1 capability to protect from αS aggregation and to modulate inflammation, and through which molecular mechanism this occurs, are being addressed in WT mice (C57Bl6) intrastriatally injected with human αS pre-formed fibrils and daily IP injected with OligoGM1 for 28 days. Specifically, the objectives of this project are *i)* to evaluate the effect of OligoGM1 on αS aggregation; *ii)* to evaluate the effect of OligoGM1 on neuronal inflammation; *iii)* Identification of OligoGM1 modulated pathways. These findings will permit to understand the OligoGM1 potential against the αS fibrillation, a key event in PD, thus providing a strong support for moving the OligoGM1 as a drug candidate for PD.

Role: Principal Investigator
Project: Understanding the cellular and molecular consequences of GM3 synthase deficiency
Partner: Prof. Maria Fazzari, Milano University, Italy; Prof. Jin-Inokuchi, Osaka University, Japan; Prof. Robert Ledeen, Rutgers University
GM3 synthase enzyme catalyzes the formation of GM3 ganglioside starting from lactosylceramide, which represents the first step for the synthesis of complex gangliosides. Accordingly, the knock-out mouse model for GM3 synthase is devoid of gangliosides of series a and b (hence GM1) while it presents gangliosides of series o. Children with total GM3 synthase deficiency display neurodevelopmental impairment, while heterozygous mutations predispose to Parkinson's disease with high incidence. The objective of this project is to understand the molecular mechanism underlying GM3 deficiency in GM3 synthase knockout (ko) HEK293T cells. Lipidic profile analyses of KO cells confirmed the absence of GM3 ganglioside and the consequent accumulation of LacCer substrate of GM3 synthase. Immunoblotting analyses revealed a significant increase of LAMP1 lysosomal marker, meaning possibly that LacCer accumulation may induce lysosomal biogenesis. By exploiting fluorigenic substrates, we found that KO cells have deregulated activity of different lysosomal enzymes meaning that an impairment of lysosomal function can occur. Additionally, considering that mitochondria alterations has been described to be correlated to GM3 synthase deficiency, mitochondria abundance and function and oxidative stress will be investigated. By completing this project, we aim to understand: *i)* how cell membrane

composition can be affected in absence of GM3; *ii)* cellular and molecular events triggered by GM3 depletion and LacCer accumulation; *iii)* whether OligoGM1 administration can influence the pathological phenotype due to GM3 deficiency. In parallel, considering the efficacy of OligoGM1 treatment in *B4galnt1*$^{+/-}$ mice, we are evaluating the oligosaccharide therapeutic potential in GM3 synthase-deficient mice.

Role: CO-Principal Investigator
Project: Assessing the toxicity and the pharmacokinetics properties of GM1 oligosaccharide
Founding: Seed4Innovation (UGOV SEED4I_2021_04) and Seed4IP (TT_MIN21_SEED4IP_03)
Partners: Prof. Elena Chiricozzi, University of Milano, Italy; Neuro-sys, Gardanne, France
This research project was aimed at analysing in detail the fate of the GM1 oligosaccharide when *in vivo* administered. achieving the following objectives:
a. Study the pharmacokinetics of GM1 oligosaccharide
b. Perform toxicological screening
In vivo analyses will be preceded by *in vitro* studies aimed at understanding the metabolism and possible toxicity in a simpler system.
By concluding this project, we will identify: i. the best dose; ii. the best route of administration; iii. distribution in the body; iv. the presence of OligoGM1 derivatives as a result of its metabolism; v. excretion.
Overall, the achievement of these objectives will allow us to obtain crucial information for completing the preclinical phase and the subsequent transition to the clinical phase. The data obtained will in fact be essential to estimate a safe starting dose for human studies and to identify the parameters for clinical monitoring of potential adverse effects.

Role: Participant
Project: Role of glycan chain of ganglioside Gm1 in modulationg the neuronal signaling
Founding: Contributo liberale Banca d'Italia (UGOV_AL_RIC21ECHIR_01*) *and Mizutani Foundation for Glycoscience (UGOV_ INTLI20ECHIR_01)
Partner: Prof. Elena Chiricozzi and Prof. Maria Fazzari, Milano University, Italy
Unlike familiar forms, sporadic Parkinson's disease (sPD) has no cogent theory that summarizes the disparate data into a compelling narrative regarding its aetiology. Although various hypotheses have been suggested, none has successfully reconciled the collected data that explain the diverse central and peripheral manifestations of sPD. Accumulating evidence is pointing out a central role for gangliosides, previously considered potential therapeutic agents and, only recently, as putative initiators (via subnormal levels) of PD pathogenesis. This pertains especially to GM1, which exhibits progressive decline with advancing age that eventually leads to neuropathological dysfunction in several key areas. Accordingly, PD patients reported reduced activity of genes involved in GM1 synthesis, accompanied by a reduction of GM1 in central (CNS) and peripheral (PNS) nervous tissues, suggesting a systemic GM1 deficiency which could explain both CNS/PNS involvement. Besides these clinical outcomes, the consequences of GM1 insufficiency are illustrated in a newly presented mouse model of sPD that was obtained from the heterozygous disruption of the B4galnt1 gene causing a reduction in GM1 content, a condition sufficient for these mice to accurately recapitulate PD phenotype: motor dysfunctions, CNS/PNS lesions and alpha-synuclein (αS) accumulation. In this scenario, the essential role of GM1 in neuronal differentiation, protection and restoration is absolute a milestone. Despite this evidence, the molecular mechanism to explain its implication in PD pathogenesis still remains to be elucidated.
Recently, we showed in neuronal cells that, within the entire GM1 molecule, the oligosaccharide chain (OligoGM1) is the actual moiety responsible for GM1 neurotrophic properties. OligoGM1 directly interacts with the NGF receptor TrkA, leading to ERK1/2 downstreaming pathway activation, to cell differentiation and to sustain neuroprotection from MPTP toxicity. Following its injection in WT mice, OligoGM1 was found to reach brain areas, and by using an in vitro BBB model, OligoGM1 showed a 20-fold higher crossing rate than that of entire GM1. Importantly, OligoGM1 systemically administered to *B4galnt1*$^{+/-}$ mice was found to completely rescue the physical symptoms, reduce αS aggregates, recover tyrosine hydroxylase neurons and restore striatal dopamine/dopac/norepinephrine levels. Proteomic analysis revealed a broad spectrum of molecular events prompted by OligoGM1 involving calcium regulation, antioxidant mechanism, mitochondrial bioenergetics, and anti-inflammatory response. Altogether, these evidences validate that the specific role of ganglioside GM1 in neuronal homeostasis is mediated by its oligosaccharide: this bioactive portion, protruding in the extracellular environment, acts at the cell surface by a direct interaction with specific proteins.
Our hypothesis is that the sPD pathogenesis is fundamentally due to plasma membrane (PM) GM1 deficiency that causes the alteration/loss of molecular interaction between OligoGM1 and specific proteins, triggering to the gradual impairment of several functions.
Two targets have commanded special attention regarding PD: neuroprotective signaling via neurotrophic receptors and αS interaction. We suggest that the reduced level of GM1, and hence of OligoGM1, in PD neurons

could trigger the neurodegenerative process by a failure in trophic signals together with a reduction of αS clearance. In this frame, the project is aimed to understand mechanistically how the progressive reduction of PM GM1 oligosaccharide triggers the loss of neurotrophic signaling and αS accumulation. 3 main objectives have been persuaded within this project: i) elucidate whether the αS accumulation onset is related to the OligoGM1; ii) verify the OligoGM1 ability to modulate neurotrophic pathways, in which GM1 role has been well defined in relation to both physiological and pathological (PD) status and iii) verify whether OligoGM1 could improve the pathological phenotype of PD model considering mitochondrial impairment and αS toxicity rescue.

Role: Partecipant
Project: Unveiling GM1-oligosaccharide role in counteracting the mitochondria impairment
Founding: Prin 2022 (UGOV PRIN202223ECHIR_01)
Partners: Prof. Elena Chiricozzi, University of Milano, Italy; Dr. Andrea Magrì, Catania University, Italy; Prof. Rober Ledeen, Rutgers University, Newark, NJ, US; Dr. Michael Speeding, Speeding Reaserch Solution, France; Neuro-sys, Gardanne, France
This line of research is developed in relation to mitochondria dysfunction within neurodegenerative disease and it is aimed at studying the mitochondria modulation upon GM1 oligosaccharide (OligoGM1) administration. Several neurodegenerative diseases, including Parkinson's disease (PD) and Amyotrophic Lateral Sclerosis (ALS), are characterized by mitochondria (mit) dysfunction which parallelly leads to a decrease of mit bioenergetics (ATP production), an increase of oxidative stress and disruption of calcium homeostasis, leading to the neuronal death. By biochemical and proteomic approaches, we found that OligoGM1 acts as mit regulator that by inducing mit genesis and enhancing mit activity can counteract mit impairment in Neuro2a (N2a) neuroblastoma cells (**Fazzari, Lunghi *et al* 2020 *Glycoconj J***). Moreover, we recently demonstrated that OligoGM1 is able to protect neuroblastoma N2a cells and primary DA neurons exposed to MPTP, a neurotoxin affecting mitochondria function (**Chiricozzi, Lunghi *et al* 2019 *Mol. Neurobiol***).
Considering the role of OligoGM1 as a regulator of mitochondria, I am currently evaluating whether OligoGM1 is able to modulate mitochondrial function in different neurodegenerative diseases such as PD and ALS.
Regarding PD, I am examining the ability of OligoGM1 to stimulate biogenesis and mitochondrial activity, to protect against oxidative stress and to activate biochemical pathways responsible for neuroprotection using *in vitro* and i*n vivo* models (MPTP and *B4galnt1*$^{+/-}$ model).
On the other hand, using motor neurons (MNs) from SOD1^{G93A} rats, a model of ALS in which the pathology is due to toxic gain-of-function of superoxide dismutase 1 (SOD1), I observed that OligoGM1 pre-treatment significantly increases neuronal survival and preserves the neuritic network in both wt and SOD1^{G93A} MNs intoxicated with glutamate. Furthermore, OligoGM1 resulted in a significant reduction of mislocalisation from the nucleus to the cytoplasm of TDP-43, a protein that represents the major component of toxic ubiquitinated protein inclusions in the cytoplasm of MNs in ALS. Finally, administration of OligoGM1 led to a significant recovery of the mitochondrial network that was impaired by glutamate exposure and to the reduction of mitochondrial superoxide anion content (**Lunghi et al 2023 *FEBS OpenBio***).

Role: Participant
Project: GM1-oligosaccharide as a new drug candidate for Rett syndrome
Founding: LEUJEUNE Foundation (UGOV_INTLI21ECHIR_01)
Partner: Prof. Elena Chiricozzi, Prof. Maria Fazzari and Prof. Nicoletta Landsberger, Milano University, Italy
Rett syndrome (RTT) is a severe neurodevelopmental disorder mainly caused by MECP2 mutations. Due to poor understanding of the molecular consequences of MECP2 deficiency, currently no cure exists. Different studies led to the identification of some molecular pathways and cellular functions compromised in RTT, including neurotrophins' signaling and mitochondrial bioenergetics. Such impairments could be linked to the depletion of a specific plasma-membrane lipid, the ganglioside GM1. GM1 has a crucial role for neuronal homeostasis maintenance acting via modulation of neurotrophins' signaling and of mitochondrial function. It should be noted that a significant reduction in GD1a level, GM1 precursor at plasma membrane, was observed in both RTT patients and mice. It is therefore likely that GM1 deficiency at plasma membrane could positively correlate with neurotrophic and mitochondrial impairment observed in RTT. Given the recent *in vitro* and *in vivo* discovery that the free soluble GM1 oligosaccharide (OligoGM1) is the bioactive portion of GM1 responsible for neurotrophic functions, we hypothesize that the plasma-membrane GM1 deficiency significantly contributes to RTT pathogenesis due to the alteration/loss of molecular interactions between the GM1-oligosaccharide and cell surface proteins that support neurotrophic signaling. By performing MitoSOX-red staining, we found an enhanced ROS production in RTT neurons that was significantly recovered by OligoGM1 treatment for 7 days. Additionally, OligoGM1 administration induced an increase of electron transport flow complexes expression which are downregulated in RTT neurons, possibly indicating a boosting of

mitochondrial activity. By analysing confocal images, we found that Mecp2-ko neurons have a reduced expression of both synapsin1/2 and shank2 markers, while OligoGM1 administration for 14 days was able to significantly increase their levels, meaning that OligoGM1 can reverts defects both at the pre- and the post-synaptic compartments.
Importantly, OligoGM1 systemically injected to RTT mice was able to counteract the worsening of the motor defect evaluated through rotarod test by recovering reduced TrkB/TrkA activation and increasing BDNF expression.
Our preliminary data support our idea that OligoGM1 can be a promising drug candidate for RTT, able to counteract the disease progression possibly acting through the stimulation of Trk signaling and the modulation of mitochondrial function. By completing this project, we will provide information about the efficacy of OligoGM1 in RTT, assessing the i) mechanism of action, ii) the capability to modulate specific neuronal functions and iii) to recover neuronal defects and physical impairments typical of the syndrome.

Role: Participant
Project: role of β-glucocerebrosidase deficiency in the onset of neuronal degeneration
Founding: Ministero dell'Università e della Ricerca-PRIN 2017 (PRIN 201719MAURE_01); Ministero dell'Università e della Ricerca-PRIN 2022 (CUP G53D23004470006); MIZUTANI FOUNDATION (ref n° 22054)
Partner: Prof. Massimo Aureli, Milano University, Italy
β-glucocerebrosidase (GCase) is a lysosomal glycohydrolase encoded by the GBA gene, responsible for the catabolism of the sphingolipid glucosylceramide (GlcCer). Deficiency of this enzyme is responsible for the lysosomal accumulation of GlcCer, leading to the onset of GCase-related pathologies that are characterized by neurodegeneration and comprise Gaucher Disease (GD) and GBA-dependent Parkinson's disease (GBA-PD). This project consists in the evaluation of molecular mechanisms at the basis of neurodegeneration occurring in GD and in GBA-PD. To investigate this linkage, I developed an *in vitro* model of the neuronal form of GD represented by iPSCs-derived dopaminergic neurons, obtained from healthy subjects, treated with CBE, a specific inhibitor of β-glucocerebrosidase (GCase). I found that CBE-treated neurons present a progressive and time-dependent accumulation of glucosylceramide (GlcCer) at lysosomal level. Moreover, CBE-treated neurons showed a neurodegenerative phenotype and an increased lysosomal biogenesis and exocytosis, the latter responsible for a modification of the lipid and protein composition of the plasma membrane that could leads to the neuronal damage (**Lunghi *et al* 2021 *Cells***). Moreover, considering the central role of lysosomes in the recycling of metabolites, I investigate the effect of the lysosomal impairment, due to glucosylceramide accumulation, on the metabolic flow through targeted metabolomics analysis by LC-MS/MS. I found an alteration in the glucose metabolism, with a slow-down of both the glycolytic pathway and Krebs cycle, and in the content of amino acids, used as alternative energy source. The use of dopaminergic neurons and midbrain organoids derived from iPSCs obtained from PD and GD-PD patients will be used to confirm the hypothesised molecular mechanism.

Role: Participant
Project: SARS-CoV-2 hampers dopamine production in iPSC-derived dopaminergic neurons
Partner: Prof. Massimo Aureli, Milano University, Italy; Prof. Claudio Fenizia, Milano University, Italy
Increasing evidence related to the onset of neurological symptoms is emerging from a high proportion of patients affected by COVID-19 pathology, suggesting the possible neuroinvasiveness of SARS-CoV-2. Recent studies show that an increasing number of patients, even with mild COVID-19, experiences symptoms even weeks or months after the infection. These symptoms comprise a wide range of neurological conditions such as memory and cognitive dysfunction, brain fog, headaches, insomnia, balance and speech issues, anxiety, and depression. These premises suggest that SARS-CoV-2 infection is not restricted to the respiratory system but reaches also the central nervous system. Particularly, in light of the COVID-19-related symptomatology, it has been hypothesized that SARS-CoV-2 might affect dopaminergic neurons. However, no scientific evidence has been produced so far. To investigate this aspect, human iPSCs were differentiated into dopaminergic neurons and infected with three different SARS-CoV-2 variants (EU, Delta and Omicron). The infection with EU and Delta variants, but not with Omicron, was responsible for a reduced intracellular content and extracellular release of dopamine. Moreover, neurons infected with EU SARS-CoV-2 were characterized by a reduced protein levels of Tyrosine hydroxylase and *dopamine transporter (DAT)* together with a reduced mRNA expression of DOPA-decarboxylase and DAT and an increase in VMAT2 transporter. In addition, the infected neurons displayed the onset of neurodegeneration, demonstrated by the reduction in MAP2 and TAU content. Finally, we found an intense activation of antiviral intracellular innate response and an increase in neuronal stress markers **(Lunghi *et al.* 2023 *Experimental and Molecular Pathology*)**. These preliminary observations let us to speculate that neurons are affected by SARS-CoV-2 infection, with particular consequences on the dopamine production and metabolism, explaining some of the neurological symptoms developed upon SARS-CoV-2 infection.

ATTIVITÀ DI RELATORE A CONGRESSI E CONVEGNI NAZIONALI E INTERNAZIONALI

August 27-September 1, 2023	26th International Glycoconjugate Symposium Title: "Glucosylceramide lysosomal accumulation leads to metabolic alterations that could underlie neuronal degeneration in GCase-related pathologies"	Taipei, Taiwan
September 1-September 2, 2023	26th International Glycoconjugate Symposium- Post-Symposium Satellite Meeting GlycoNeuro Title: "The neuroprotective role of the oligosaccharide of ganglioside GM1 in Parkinson's disease	Taipei, Taiwan
September 28-30, 2022	5th *BraYn "*Brainstorming Research Assembly for Young Neuroscientists" Title: "New insights into the effects of Sars-COV-2 infection on nervous system: alteration of dopamine metabolism in iPSCs-derived dopaminergic neurons"	Rome, Italy
March 27-April 01, 2022	Gordon Research Conference on Glycolipid and Sphingolipid Biology Title: "Role of ß-glucocerebrosidase deficiency in the onset of neuronal degeneration: new findings on the involvement of a lysosome-plasma membrane axis"	Lucca, Italy
June 22, 2021	BIOMETRA SEMINAR- University of Milano Title: "Sphingolipids and neurodegeneration: a focus on Parkinson's disease"	Milano, Italy
September 1-4, 2019	ESN Biennial Conference Title: "GM1 oligosaccharide modulation of calcium signaling in neuronal functions"	Milano, Italy
June 3-7, 2019	31th National Meeting "*A. Castellani*" of Biochemistry PhD students Title: "GM1 oligosaccharide modulation of calcium signaling in neuronal functions"	Brallo di Pregola, Pavia, Italy
April 15-17, 2018	4th Meeting of Young Biochemistry of Milano Area Title: "GM1 neuroprotective properties are related to GM1 oligosaccharide"	Gargnano, Garda, Italy
June 4-8, 2018	30th National Meeting "*A. Castellani*" of Biochemistry PhD students Title: "GM1 neuroprotective properties are related to GM1 oligosaccharide"	Brallo di Pregola, Pavia, Italy

PARTECIPAZIONE A CONGRESSI, SCUOLE E SEMINARI

Date	**Title**	**Location**
August 27-September 1, 2023	26th International Glycoconjugate Symposium - **Selected speaker** Title: "The neuroprotective role of the oligosaccharide of ganglioside GM1 in Parkinson's disease"	Taipei, Taiwan
September 1-September 2, 2023	26th International Glycoconjugate Symposium- Post-Symposium Satellite Meeting GlycoNeuro- **Selected speaker** Title: "Glucosylceramide lysosomal accumulation leads to metabolic alterations that could underlie neuronal degeneration in GCase-related pathologies"	Taipei, Taiwan
August 8-11, 2023	ISN-ESN 2023 Meeting - **Poster presentation** Title: "GM1 oligosaccharide acts as a mitochondrial modulator: implication in neurological diseases"	Porto, Portugal
July 19-24, 2023	6th Course INNOGLY WG2: THE GLYCOBIOLOGY OF CELL METABOLIC PROCESSES AT THE NANOSCALE IN HUMAN PATHOLOGY "	Erice, Sicily
September 28-30, 2022	5th *BraYn "*Brainstorming Research Assembly for Young Neuroscientists" - **Selected speaker**. Title: "New insights into the effects of Sars-COV-2 infection on nervous system: alteration of dopamine metabolism in iPSCs-derived dopaminergic neurons"	Rome, Italy
August 28-September 01, 2022	ISN-ASN Meeting - **Poster presentation** Title: "SARS-CoV-2 affects the dopamine metabolism in human iPSCs-derived dopaminergic neurons"	Honolulu, USA

March 27-April 01, 2022	Gordon Research Conference on Glycolipid and Sphingolipid Biology - **Selected Speaker.** Title: "Role of ß-glucocerebrosidase deficiency in the onset of neuronal degeneration: new findings on the involvement of a lysosome-plasma membrane axis"	Lucca, Italy
March 15-20, 2022	16th International Conference on Alzheimer's and Parkinson's Diseases - **Poster presentation** Title: "The neuroprotective role of GM11-oligosaccharide in Parkinson's disease"; "Dissecting the role of glucosylceramide accumulation in the neuronal damage occurring in GBA-related pathologies"	Barcelona, Spain
October 20-22, 2021	4th *BraYn "*Brainstorming Research Assembly for Young Neuroscientists" - **Poster presentation** Title: "Dissecting the molecular mechanism linking GCase deficiency with the onset of neurodegeneration in Gaucher and Parkinson's diseases"	virtual
September 19-26, 2021	First ESN-ISN advanced School - **Poster presentation**. Title: "GM1 oligosaccharide role in preventing α-synuclein aggregation"	Athens, Greece
July 3-8, 2021	45th FEBS virtual Congress - **Poster presentation** Title: "GM1-oligosaccharide neuroprotective action in *in vitro* and *in vivo* models of Parkinson's Disease"	virtual
June 22, 2021	BIOMETRA SEMINAR - **invited speaker** Title: "Sphingolipids and neurodegeneration: a focus on Parkinson's disease"	Milano, Italy
May 25-26, 2021	1st ESN virtual Conference - **Poster presentation** Title: "The oligosaccharide portion of ganglioside GM1 displays neuroprotective properties in *in vitro* and *in vivo* models of Parkinson's Disease"	virtual
May 20-21, 2021	1st online meeting of the Group "Proteine" of the Italian Society for Biochemistry and Molecular Biology - **Poster presentation** Title: The multitasking role of GM1 oligosaccharide in modulating neuronal intracellular signalling" 1st online meeting of the Group "Proteine"	virtual
September 1-4, 2019	ESN Biennial Conference - **selected speaker** Title: "GM1 oligosaccharide modulation of calcium signaling in neuronal functions"	Milano, Italy
August 25-31, 2019	25th International Symposium on Glycoconjugates - **Poster presentation** Title: "GM1 oligosaccharide modulation of calcium signaling in neuronal functions"	Milano, Italy
August 4-8, 2019	ISN-ASN Meeting - **Poster presentation** Title: "GM1 oligosaccharide is the active portion responsible for GM1 neuroprotective properties"	Montréal, Canada
March 26-31, 2019	AD/PD 14th Conference	Lisbon, Portugal
September 10-15, 2018	Second ISN-JNC Flagship School - **Poster presentation** Title: The oligosaccharide portion of ganglioside GM1 as a new neurotrophic player	Alpbach, Austria
July 7-12, 2018	43rd FEBS Congress - **Poster presentation** Title: "GM1 neuroprotective properties are related to GM1 oligosaccharide"	Prague, Czech Republic
September 23, 2019	4th Workshop of the Department of Medical Biotechnologies and Translational Medicine (BIOMETRA)- **Poster presentation** Title: "GM1 oligosaccharide modulation of calcium signaling in neuronal functions"	Milano, Italy
June 3-7, 2019	31th National Meeting "*A. Castellani*" of Biochemistry Ph. D. student -**selected speaker** Title: "GM1 oligosaccharide modulation of calcium signaling in neuronal functions"	Brallo di Pregola, Pavia, Italy
June 23-25, 2019	5th Meeting of Young Biochemistry from the Lombardy Area - **Poster presentation** Title: "La storia dell'OligoGM1: un percorso dal banco di laboratorio verso la clinica"	Gargnano, Garda, Italy
September 24, 2018	3rd Workshop of Department of Medical Biotechnology and Translational Medicine (BIOMETRA) - **Poster presentation** Title: "Role of GM1 oligosaccharide in neuroprotection"	Milano, Italy

April 15-17, 2018	4th Meeting of Young Biochemistry of Milano Area - **selected speaker** Title: "GM1 neuroprotective properties are related to GM1 oligosaccharide"	Gargnano, Garda, Italy
June 4-8, 2018	30th National Meeting "*A. Castellani*" of Biochemistry Ph. D. student - **selected speaker** Title: "GM1 neuroprotective properties are related to GM1 oligosaccharide"	Brallo di Pregola, Pavia, Italy
September 26, 2017	2nd Workshop of Department of Medical Biotechnology and Molecular Medicine (BIOMETRA)	Milano, Italy
June 25-27, 2017	3th Meeting of Young Biochemistry of Milano Area - **Poster presentation** Title: "Development of a new in vitro model to study the role of GBA impairment in the onset of Parkinson's disease"	Gargnano, Garda, Italy
February 2, 2017	Neuroscience network at La Statale, NEURO-NEST	Milano, Italy

CONSEGUIMENTO DI PREMI E RICONOSCIMENTI NAZIONALI E INTERNAZIONALI PER ATTIVITÀ DI RICERCA

Year	**Award description**
2023	Travel award - 26th International Glycoconjugates Symposium, Taipei, Taiwan, August 27-September 2, 2023
2023	Travel award - ISN-ESN 2023 Meeting, Porto, Portugal, August 8-11, 2023
2022	Travel award - ISN-ASN Meeting, Honolulu, August 28 - September 1, 2022
2022	Travel award - 24th Biennial Meeting of the European Society for Neurochemistry and 8th Conference on "Molecular and Cellular Mechanisms of Regulation in the Nervous System" planned to be St. Petersburg, Russia, May 22-25, 2022
2021	Travel award – First ESN-ISN advanced school, Athens, Greece, September 19-26, 2021
2021	Travel award- 45th FEBS Congress, July 3-8, 2021
2019	Travel award- ESN Biennial Conference, Molecular Mechanism of Regulation of the Nervous System, Milano, Italy, September 1-4, 2019
2019	Travel award- ISN-ASN Meeting, Montréal, August 4-8, 2019
2019	Italian Society of Biochemistry and Molecular Biology award – Best Poster Presentation. 5th Meeting of Young Biochemists of Lombardia region, Gargnano, Italy, June 23-25, 2019
2018	Travel award- 43rd FEBS Congress, Prague, July 7-12, 2018
2018	Travel award- Second ISN-JNC Flagship School, Alpbach, Austria, September 10-15, 2018
	Fellowship description
2022-2025	Postdoctoral fellowship type A. Department of Medical Biotechnology and Translational Medicine, University of Milano, Italy. Total amount: 63000 euro
2020-2022	Postdoctoral fellowship type B. Department of Medical Biotechnology and Translational Medicine, University of Milano, Italy. Total amount: 48000 euro
2017-2020	PhD fellowship at Department of Medical Biotechnology and Translational Medicine, University of Milano, Italy. Total amount: 49050 euro
	Grant description
2023	EMBO Scientific Exchange Grant- 6300 euro
2023	ISN International Travel Support (ITS)- 4000 USD
2023	BRAYN Trainee Travel Grant "PLACIDO ILLIANO"- 500 euro
2021	Milano University, Seed4Innovation program 2021/2022 – 50000 euro
2021	Italian Ministry of Economic Development, Seed4Innovation_PoCe_MISE program 2021/2022- 40000 euro

ATTIVITÀ DI REVISIONE E DI REDAZIONE

2023 – To date Reviewer for *Frontiers in Molecular Neuroscience*
2023 – To date Reviewer for *Pharmaceutics-MDPI* journal
2023 – To date Reviewer for *Glycoconjugates Journal*
2023 – To date Reviewer for *Cells-MDPI* journal
2022 – To date Reviewer for *IJMS-MDPI* journal
2022 – To date Reviewer for *Molecules-MDPI* journal
2023 – Guest Editor for a Special Issue in *Biomedicines-MDPI* journal ""Sphingolipid Metabolism and Signaling in Health and Diseases"

ORGANIZZAZIONE DI CONGRESSI E SEMINARI

7th BioMeTra Workshop, September 19th, 2023
Department of Medical Biotechnology and Translational Medicine, University of Milano, Lita, Segrate, Milano (MI), Italia – *Local committee*

BioMeTra Seminars 2022-2023
Department of Medical Biotechnology and Translational Medicine, University of Milano, Lita, Segrate, Milano (MI), Italia – *Scientific committee*

APPARTENENZA A SOCIETÀ SCIENTIFICHE

2018 – To date Associated member of International Society for Neurochemistry (ISN)
2018 – To date Associated member of Italian Society of Biochemistry (SIB)
2018 – To date Associated member of European Society for Neurochemistry (ESN)
2021 – To date Associated member of BraYn association

ATTIVITA' DI DISSEMINAZIONE SCIENTIFICA

Third mission for University of Milano: activities in primary schools in Milano and neighboring municipalities to describe with a lay language the principle of biochemistry, 2017-2024

MeetMeTonight, "Run into the cell" - September 28-29, 2018

MeetMeTonight "Viaggio al centro della cellula" - September 29-30, 2017

MeetMeTonight, "Viaggio al centro della cellula" - September 25-26, 2015

PRODUZIONE SCIENTIFICA

PUBBLICAZIONI SCIENTIFICHE

My research activity (2018-2024) is documented by 29 peer reviewed full articles in international journals, with 363 citations and with an h-index of 12 (Scopus January 2024). I have the first authorship in 11 of those publications and the last authorship in 2 of those publications. Moreover, my research was reported in 49 international congress communications, 22 of them published on the Special Issues of international scientific journals.

Books

1. Aureli M, Mauri L, Carsana EV, Dobi D, Breviario S, **Lunghi G**, Sonnino S. Gangliosides and Cell Surface Ganglioside Metabolic Enzymes in the Nervous System. Adv Neurobiol. 2023;29:305-332. doi: 10.1007/978-3-031-12390-0_11. PMID: 36255680.
2. **G. Lunghi**, E.V. Carsana, N. Loberto, S. Sonnino, M. Aureli (2021) Lysosomes-neuronal degeneration in lysosomal storage disorders. In: Hamano T and Mutoh T (Eds). Autophagy Dysfunction in Alzheimer's Disease and Dementia. San Diego: Elsevier Inc./Academic Press, 2022: 25-40. Paperback ISBN: 9780323899062
3. E. Chiricozzi, M. Aureli, L. Mauri, E. Di Biase, **G. Lunghi**, M. Fazzari, M. Valsecchi, E.V. Carsana, N. Loberto, A. Prinetti, S. Sonnino (2021) Glycosphingolipids. Advances in Experimental Medicine and Biology, Springer. 1325, https://doi.org/10.1007/978-3-030-70115-4_3
4. Loberto N, **Lunghi G**, Schiumarini D, Samarani M, Chiricozzi E, Aureli M (2018) Methods for Assay of Ganglioside Catabolic Enzymes. Methods Mol Biol. 1804:383-400. doi: 10.1007/978-1-4939-8552-4_18

Articles

1. Fazzari M, **Lunghi G**, Di Biase E, Maggioni M, Carsana EV, Cioccarelli L, Vigani L, Loberto N, Aureli M, Mauri L, Ciampa MG, Valsecchi M, Takato K, Imamura A, Ishida H, Ben Mariem O, Saporiti S, Palazzolo L, Chiricozzi E, Eberini I, Sonnino S. GM1 structural requirements to mediate neuronal functions. Glycoconj J. 2023 Dec 15. doi: 10.1007/s10719-023-10141-8. Epub ahead of print. PMID: 38100017. ***Giulia Lunghi is co-first author***
2. **Lunghi G**, Di Biase E, Carsana EV, Henriques A, Callizot N, Mauri L, Ciampa MG, Mari L, Loberto N, Aureli M, Sonnino S, Spedding M, Chiricozzi E, Fazzari M. GM1 ganglioside exerts protective effects against glutamate-excitotoxicity via its oligosaccharide in wild-type and amyotrophic lateral sclerosis motor neurons. FEBS Open Bio. 2023 Oct 27. doi: 10.1002/2211-5463.13727. Epub ahead of print. PMID: 37885330.
3. Cappelletti G, Carsana EV, **Lunghi G**, Breviario S, Vanetti C, Di Fonzo AB, Frattini E, Magni M, Zecchini S, Clerici M, Aureli M, Fenizia C. SARS-CoV-2 hampers dopamine production in iPSC-derived dopaminergic neurons. Exp Mol Pathol. 2023 Sep 30;134:104874. doi: 10.1016/j.yexmp.2023.104874. Epub ahead of print. PMID: 37775022. ***Giulia Lunghi is co-first author***
4. Fazzari M, Di Biase E, Zaccagnini L, Henriques A, Callizot N, Ciampa MG, Mauri L, Carsana EV, Loberto N, Aureli M, Mari L, Civera M, Vasile F, Sonnino S, Bartels T, Chiricozzi E, **Lunghi G**. GM1 oligosaccharide efficacy against α-synuclein aggregation and toxicity in vitro. Biochim Biophys Acta Mol Cell Biol Lipids. 2023 Sep;1868(9):159350. doi: 10.1016/j.bbalip.2023.159350. Epub 2023 Jun 16. PMID: 37330108.
5. Fazzari M, **Lunghi G**, Henriques A, Callizot N, Ciampa MG, Mauri L, Prioni S, Carsana EV, Loberto N, Aureli M, Mari L, Sonnino S, Chiricozzi E, Di Biase E. GM1 Oligosaccharide Efficacy in Parkinson's Disease: Protection against MPTP. Biomedicines. 2023 Apr 28;11(5):1305. doi: 10.3390/biomedicines11051305. PMID: 37238977; PMCID: PMC10216367. ***Giulia Lunghi is co-first author***.
6. Dobi D, Loberto N, Bassi R, Pistocchi A, **Lunghi G**, Tamanini A, Aureli M. Cross-talk between CFTR and sphingolipids in cystic fibrosis. FEBS Open Bio. 2023 Sep;13(9):1601-1614. doi: 10.1002/2211-5463.13660. Epub 2023 Jun 22. PMID: 37315117; PMCID: PMC10476574.
7. **Lunghi G**, Fazzari M, Ciampa MG, Mauri L, Di Biase E, Chiricozzi E, Sonnino S. Regulation of signal transduction by gangliosides in lipid rafts: focus on GM3-IR and GM1-TrkA interactions. FEBS Lett. 2022 Dec;596(24):3124-3132. doi: 10.1002/1873-3468.14532. Epub 2022 Nov 11. PMID: 36331354.
8. **Lunghi G**, Carsana EV, Loberto N, Cioccarelli L, Prioni S, Mauri L, Bassi R, Duga S, Straniero L, Asselta R, Soldà G, Di Fonzo A, Frattini E, Magni M, Liessi N, Armirotti A, Ferrari E, Samarani M, Aureli M. β-Glucocerebrosidase Deficiency Activates an Aberrant Lysosome-Plasma Membrane Axis Responsible for the Onset of Neurodegeneration. Cells. 2022 Jul 29;11(15):2343. doi: 10.3390/cells11152343. PMID: 35954187; PMCID: PMC9367513.
9. Carsana, E.V.; Audano, M.; Breviario, S.; Pedretti, S.; Aureli, M.; **Lunghi, G**.; Mitro, N. Metabolic Profile Variations along the Differentiation of Human-Induced Pluripotent Stem Cells to Dopaminergic Neurons. Biomedicines 2022, 10, 2069. https://doi.org/10.3390/biomedicines10092069. **Lunghi *Giulia is co-last author***.
10. Carsana EV, **Lunghi G**, Prioni S, Mauri L, Loberto N, Prinetti A, Zucca FA, Bassi R, Sonnino S, Chiricozzi E, Duga S, Straniero L, Asselta R, Soldà G, Samarani M, Aureli M. Massive Accumulation of Sphingomyelin Affects the Lysosomal and Mitochondria Compartments and Promotes Apoptosis in Niemann-Pick

Disease Type A. J Mol Neurosci. 2022 Jun 21. doi: 10.1007/s12031-022-02036-4

11. Kakouri AC, Votsi C, Oulas A, Nicolaou P, Aureli M, **Lunghi G**, Samarani M, Compagnoni GM, Salani S, Di Fonzo A, Christophides T, Tanteles GA, Zamba-Papanicolaou E, Pantzaris M, Spyrou GM, Christodoulou K. Transcriptomic characterization of tissues from patients and subsequent pathway analyses reveal biological pathways that are implicated in spastic ataxia. Cell Biosci. 2022 Mar 11;12(1):29. doi: 10.1186/s13578-022-00754-1

12. Fazzari M, **Lunghi G**, Chiricozzi E, Mauri L, Sonnino S. Gangliosides and the Treatment of Neurodegenerative Diseases: A Long Italian Tradition. Biomedicines. 2022 Feb 2;10(2):363. doi: 10.3390/biomedicines10020363. ***Giulia Lunghi is co-first author***

13. Fazzari M, Di Biase E, **Lunghi G**, Mauri L, Chiricozzi E, Sonnino S. Novel insights on GM1 and Parkinson's disease: A critical review. Glycoconj J. 2022 Jan 22. doi: 10.1007/s10719-021-10019-7.

14. **Lunghi G**, Fazzari M, Di Biase E, Mauri L, Sonnino S, Chiricozzi E (2021) The structure of gangliosides hides a code for determining neuronal functions. FEBS Open Biology 2021 May 18. doi: 10.1002/2211-5463.13197.

15. Chiricozzi E, Di Biase E, **Lunghi G**, Fazzari M, Loberto N, Aureli M, Mauri L, Sonnino S (2021) Turning the spotlight on the oligosaccharide chain of GM1 ganglioside. Glycoconjugate Journal 2021 Feb;38(1):101-117. doi: 10.1007/s10719-021-09974-y.

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ATTI DI CONVEGNO

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