

BIOGRAPHICAL SKETCH

NAME	ANGELA GRITTI		
POSITION TITLE	Group Leader Gene/Neural Stem Cell Therapy for Lysosomal Storage Diseases (LSD) San Raffaele Telethon Institute for Gene Therapy (SR-Tiget) San Raffaele Scientific Institute, Milan Italy. Associate Professor of Histology Vita-Salute San Raffaele University, Milan, Italy		
EDUCATION/TRAINING			
University of Milan, Italy	Master degree in Biological Sciences (summa cum laude)	1990	Biological Sciences, Pharmacology
Italy	Qualification to practice as a biologist	1991	
University of Milan, Italy	Specialty in Toxicology (70/70)	1996	Toxicology
University of Turin, Italy	PhD in Basic Sciences and Veterinary Biotechnology (XVIII cycle)	2006	Neuroscience, comparative neurogenesis, neural stem cells
Italy	National Academic Qualification as Associate Professor	2018	05/H2 - Histology

PERSONAL STATEMENT

As a Principal Investigator at Ospedale San Raffaele (OSR), San Raffaele Telethon Institute for Gene Therapy (SR-Tiget, Milan), I coordinate a group of 12 people in the "Unit of gene/neural stem cell therapy for Lysosomal storage diseases (LSD)." The overarching goal of the lab is to study and treat rare genetic diseases affecting the CNS, with a particular focus on Lysosomal Storage Disorders (LSDs), including leukodystrophies - Metachromatic leukodystrophy (MLD), Globoid cell Leukodystrophy (GLD) and Alexander's disease (AxD) - and GM2 gangliosidosis - Sandhoff Disease (SD) and Tay-Sachs Disease (TSD). Our projects span basic to translational research, using murine and human models and testing different therapeutic platforms (i.e., cell therapy, *in vivo* and *ex vivo* gene therapy, gene addition, genome- and epigenome editing). A critical part of our research is devoted to studying the early pathogenic events due to genetic defects and the therapeutic mechanisms of disease correction upon treatments to refine and implement the gene therapy strategies under testing. To address this issue, we are exploiting several *in vitro* systems, including patient-specific iPSC-derived neural populations (2D and 3D models), which recapitulate key biochemical features of the disease and allow for the identification of early defects in human neuronal/glia cell populations that were previously overlooked or not studied at all.

As an assistant professor of Human Histology at the Univ. Vita-Salute San Raffaele, Milan, Master's degree in Medicine and Surgery and International MD program, I combine frontal and practical lessons and promote the active participation of students through interactive group discussions. My goal is to provide a comprehensive overview of the primary tissue types and subtypes, their developmental origin, function, maintenance, and contribution to organs and systems, addressing from a scientifically informed standpoint the recent advances in stem cell manipulation, tissue replacement, and regeneration while highlighting their current limitations and significant gaps in our knowledge.

EMPLOYMENT AND EXPERIENCE

01.05.2024-present	Assistant Professor of Human Histology, Vita-Salute San Raffaele University, Milan, Italy
2006-present	Group Leader , Unit of Gene/neural stem cell therapy for lysosomal storage diseases, San Raffaele Telethon Institute for Gene Therapy (SR-Tiget; Dir. L. Naldini), Ospedale San Raffaele (OSR), Milan, Italy
2001-2005	Research Scientist , Stem Cell Research Institute (SCRI; Dir. G. Cossu), San Raffaele Scientific Institute, Milan, Italy
2000	Fellow , American Spinal Cord Society
1997-1999	Level I biologist manager , National Neurological Institute "C.Besta", Milan, Italy
1995-1997	Senior fellow , Neuropharmacology, National Neurological Institute "C.Besta", Milan, Italy
1991-1994	Junior fellow , Neuropharmacology, National Neurological Institute "C.Besta", Milan, Italy
1992	Visiting scientist , Faculty of Medicine, the University of Calgary, Alberta, Canada (Supervisor Prof. S. Weiss).

TEACHING AND MENTOR ACTIVITIES

2016-present	Adjunct professor, Human Histology (course coordinator from 2019/2020), School of Medicine, Master's degree in Medicine and Surgery and International MD Program, Univ. Vita-Salute San Raffaele, Milan, Italy.
2016-2022	Lecturer, course "Organellar Pathology", School of Medicine, Master degree in Medical, Molecular and Cellular Biotechnology, Univ. Vita-Salute San Raffaele. Topic: "Lysosomes: a multifunctional organelle" (2h)
2011-present	Lecturer, Gene Therapy Course, School of Medicine, Master's degree in molecular and cellular medical biotechnology, Univ. Vita Salute San Raffaele, Milan, Italy. Topic: Gene therapy of Lysosomal storage diseases (2h)
2002-2003	Adjunct Professor, Biology, University of Milan, Faculty of Psychology
2001-2002	Adjunct Professor, Cell Biology, University of Milan, Faculty of Biological Science

ACADEMIC SUPERVISION

2002-present Advisor/Mentor of master students (22, including 1 student within the Erasmus+ program), Ph.D. students (12), Post-Laurea fellows (11), and project leaders (1).

PROFESSIONAL ACTIVITIES AND COMMISSION OF TRUST

Scientific committees (member): AFM-Telethon, Strategic and Therapeutic Orientation Committee (2015); Italian Telethon Foundation, Patent Committee (2015-2016); ASGCT Neurologic & Ophthalmic Gene & Cell Therapy committee (2022-2025; chair for the year 2024).

Grant reviewer: ERC starting grants, LS7 panel member (2022/2024); Italian Multiple Sclerosis Association; Great Ormond Street Hospital (GOSH) charity, UK; European Leukodystrophy Association (ELA), FR; The Netherlands Organization for Scientific Research (NWO); Health Research Board (HRB), IR; Sparks Children Medical Research, UK; AUSTRIAN Science Fund; Vaincre Les Maladies Lysosomales (VML), FR; AFM Telethon, FR; Istituto Superiore di Sanita' (ISS), IT; UK Research and Innovation (UKRI); Israel Science Foundation (ISF).

Abstract reviewer: American Society for Gene and Cell Therapy (ASGST), European Society for Gene and Cell Therapy (ESGCT), International Society for Stem Cell Research (ISSCR)

Journal Reviewer: Exp. Neurology; Hum Gene Ther; Eur J. of Neurosci.; J. of Neurosci.; J. of Neurochem.; Mol. Cell. Neurosci.; Stem Cells; Stem Cells Dev; Cell Death and Differ.; Dev. Neurosci.; Glia; Mol Genetics and Metab; Mol. Therapy; Mol. Therapy Meth. Clin. Dev.; Mol. Ther. Nucleic Acids; Neurobiol. of Disease; PNAS; Brain; Stem Cell Rep; Science; Cell Stem Cell; Science Transl Med; J. of Clin. Investigation (JCI); Sci. Rep.

Invited speaker at national and international conferences/lectures (**selected; 2014-2023**):

- 2023 Italian Society for Neuroscience (SINS), 20th National Congress, Torino (IT)
- 2023 The International School of Nanomedicine, E. Majorana Foundation and Centre for Scientific Culture, Erice (IT)
- 2023 European Leukodystrophy Association (ELA) family-scientist meeting, Paris (FR)
- 2022 European Leukodystrophy Association (ELA) family-scientist meeting, Paris (FR)
- 2021 2nd Achucarro International Glial School, Bilbao (ES)(remote)
- 2019 International Krabbe Think Tank London (UK), Session 3: Preclinical Data and Animal Models
- 2019 Metachromatic Leukodystrophy (MLD) Translational Res. Network Annual Meeting, Clearwater Beach, FL (USA).
- 2019 European Leukodystrophy Association (ELA)/MLD Research Group: Pathophysiology of Metachromatic Leukodystrophy, Paris (FR)
- 2018 European Leukodystrophy Association (ELA) workshop and family meeting, Paris (FR)
- 2017 Institute Imagine, Paris (FR) (host: Annarita Miccio)
- 2017 Genethon, Evry (FR)(host: Mario Amendola)
- 2017 Mediterranean Neuroscience Society, 6th Conference, Radisson BLU St Julian's, Malta
- 2017 Univ. of Milano-Bicocca, Ph.D. program in Translational and Molecular Medicine, DIMET Course "Cell Reprogramming 2.0: toward the next decade of iPSC cell biology and disease modeling".
- 2017 Fondazione Telethon XIX Scientific Convention, Riva del Garda, Italy
- 2016 ESGCT and ISSCR COLLABORATIVE CONGRESS Florence (IT), Parallel session 3b: Stem Cell Based neural disease modeling (**co-chair**).
- 2016 ECMED Workshop within the Marie Curie Training network, "The use of virus vectors in Neuroscience: virus-mediated gene-delivery into the rodent brain." Bogliasco (IT)
- 2015 European Society for Gene and Cell Therapy (ESGCT) and FSGT Collaborative Congress, Helsinki (SF).
- 2015 NEST, Istituto Nanoscienze-CNR and Scuola Normale Superiore, Pisa (IT) (host: Marco Cecchini)
- 2014 European Society for Gene and Cell Therapy (ESGCT) and NVGCT Collaborative Congress, The Hague, Netherlands

Conference organization:

- 2017 Member of the organizing committee, SR-Tiget Scientific Retreat, Camogli, Italy
- 2015 Member of the organizing committee, ELRIG Drug Discovery Meeting, Telford, UK, responsible for Track 3-Cell & Gene Therapy
- 2014 Member of the organizing committee, Course "Cellular and animal models in Neuroscience Research", Ph.D. Section of Neuroscience and Experimental Neurology, San Raffaele Scientific Institute, Milan, Italy
- 2011-12 Member of the organizing committee, San Raffaele Scientific Retreat.

Outreach activities:

- 2019, 2022 Annual Telethon Marathon (interviews with families, videos)
- 2019 Contribution to the project *Pearson Italia*: editorial contents (video+interview) realized in collaboration with Fondazione Telethon for the Biology volume (Campbell - I e II biennio)
- 2015-2018 Frontal lessons/discussions with high school students on gene therapy and the role of the researcher in society—educational activities sponsored by Fondazione Telethon.
- 2016 Invited speaker, Unistem Day . "Terapie con le cellule staminali: a che punto siamo" – Fondazione INGM "Romeo ed Enrica Invenizzi" Milan

Major ongoing collaborations:

- **Anna Kajaste-Rudnitski**, Univ di Pavia (PV), ITA
"Investigating Innate Sensing and Antiviral Restriction of AAV vectors in the Human Central Nervous System"

- **Angelo Lombardo**, Università Vita-Salute San Raffaele – Milan, ITA
“Epigenome editing in hiPSC-derived neural progenitors”
- **A. Cantore**, Università Vita-Salute San Raffaele – Milan, ITA
“Testing systemic liver-directed GT strategies in LSD murine models”
- **Eugenio Montini**, Ospedale San Raffaele - Milan, ITA
“Evaluation of the genotoxicity of gene editing approaches targeting CNS”
- **Sabata Martino**, Università di Perugia, ITA
“Analysis of lysosomal enzymatic activity in cells and tissues”
- **Massimo Aureli**, Università degli Studi di Milano -ITA
“Evaluation of the ganglioside content in LSD murine models”
- **Luigi Anastasia**, Università Vita-Salute San Raffaele and Gruppo San Donato -Milan, ITA
“Evaluation of the glycosylation pattern of lysosomal enzymes”
- **A. Miccio**, Institute Imagine, Paris-FR
“Analyses of transcriptional and epigenetic modifications in hiPSCs and neural progeny”
- **Vivi Heine**, Univ of Amsterdam Medical Center – NL
“Development of hiPSC-based models for Leukodystrophies”
- **Oliver Brustle**, Institute of Reconstructive Neurobiology LIFE & BRAIN Center Univ. Hospital of Bonn - DE
“Development of hiPSC-neural and microglial progeny”
- **Monica Sousa**, Instituto de Investigação e Inovação Em Saúde (i3S), University of Porto - PT
“Evaluation of axonal function in hiPSC-derived LSD neurons”

MEMBERSHIPS OF SCIENTIFIC SOCIETIES

From 2024	Collegio dei Docenti di Istologia ed Embriologia
2021-present	International Society for Stem Cell Research (ISSCR)
2010-present	European Society for Gene and Cell Therapy (ESGCT)
2007-present	American Society for Gene and Cell Therapy (ASGCT)

CAREER BREAKS

01/03/1996 - 31/08/1996
04/08/1998 - 04/02/1999
Maternity leave

SCIENTIFIC PRODUCTION

Source: SCOPUS, September 2023

I have published 78 papers in international peer-reviewed scientific journals (66 original papers and 12 reviews/book chapters) as first author (11), last/corresponding author (28), and co-author (39).

- Percent of documents co-authored with researchers in other countries/regions: 40.74%
- Total citations: 9.286
- *h-index*: 36

Scopus Author ID: 7004129522
ORCID ID: 0000-0002-9845-0370
Researcher ID: K-2729-2016

Complete list of publications at:

<https://www.ncbi.nlm.nih.gov/myncbi/1s4kKbQ6tb/bibliography/public/>

Selected publications (2014-2024)

1. Mangiameli E, Freschi M, Luciani M, **Gritti A**. Generation of neuronal/glia mixed cultures from human induced pluripotent stem cells (hiPSCs). *Methods Cell Biol.* 2022;171:229-245. doi: 10.1016/bs.mcb.2022.04.012. PMID: 35953203.
2. Luciani M, Garsia C, Mangiameli E, Meneghini V, **Gritti A**. Intracerebroventricular transplantation of human iPSC-derived neural stem cells (hiPSC-NSCs) into neonatal mice. *Methods Cell Biol.* 2022;171:127-147. doi: 10.1016/bs.mcb.2022.04.007. PMID: 35953197.
3. Sala D, Ornaghi F, Morena F, Argentati C, Valsecchi M, Alberizzi V, Di Guardo R, Bolino A, Aureli M, Martino S, **Gritti A**. Therapeutic advantages of combined gene/cell therapy strategies in a murine model of GM2 gangliosidosis. *Mol Ther Methods Clin Dev.* 2022 Jun 9;25:170-189. doi: 10.1016/j.omtm.2022.03.011. PMID: 35434178.
4. Giordano AMS, Luciani M, Gatto F, Abou Alezz M, Beghè C, Della Volpe L, Migliara A, Valsoni S, Genua M, Dzieciatkowska M, Frati G, Tahraoui-Bories J, Giliani SC, Orcesi S, Fazzi E, Ostuni R, D'Alessandro A, Di Micco R, Merelli I, Lombardo A, Reijns MAM, Gromak N, **Gritti A**, Kajaste-Rudnitski A. DNA damage contributes to neurotoxic inflammation in Aicardi-Goutières syndrome astrocytes. *J Exp Med.* 2022 Apr 4;219(4). doi: 10.1084/jem.20211121. PMID: 35262626
5. Cantore A, Fraldi A, Meneghini V, **Gritti A**. In vivo Gene Therapy to the Liver and Nervous System: Promises and Challenges. *Front Med (Lausanne).* 2021;8:774618. doi: 10.3389/fmed.2021.774618. Review. PubMed PMID: 35118085
6. Ricca A, Cascino F, **Gritti A**. Isolation and Culture of Neural Stem/Progenitor Cells from the Postnatal Periventricular Region. *Methods Mol Biol.* 2022;2389:11-31. doi: 10.1007/978-1-0716-1783-0_2. PMID: 34557998.

7. Mangiameli E, Cecchele A, Morena F, Sanvito F, Matafora V, Cattaneo A, Della Volpe L, Gnani D, Paulis M, Susani L, Martino S, Di Micco R, Bachi A, **Gritti A**. Human iPSC-based neurodevelopmental models of globoid cell leukodystrophy uncover patient- and cell type-specific disease phenotypes. *Stem Cell Reports*. 2021 Jun 8;16(6):1478-1495. doi: 10.1016/j.stemcr.2021.04.011. PMID: 33989519
8. Meneghini V, Peviani M, Luciani M, Zambonini G, **Gritti A**. Delivery Platforms for CRISPR/Cas9 Genome Editing of Glial Cells in the Central Nervous System. *Front Genome Ed*. 2021;3:644319. doi: 10.3389/fgeed.2021.644319. eCollection 2021. Review. PMID: 34713256
9. Ricca A, Cascino F, Morena F, Martino S, **Gritti A**. In vitro Validation of Chimeric β -Galactosylceramidase Enzymes With Improved Enzymatic Activity and Increased Secretion. *Front Mol Biosci*. 2020;7:167. doi: 10.3389/fmolb.2020.00167. eCollection 2020. PMID: 32850960
10. Ornaghi F, Sala D, Tedeschi F, Maffia MC, Bazzucchi M, Morena F, Valsecchi M, Aureli M, Martino S, **Gritti A**. Novel bicistronic lentiviral vectors correct β -Hexosaminidase deficiency in neural and hematopoietic stem cells and progeny: implications for in vivo and ex vivo gene therapy of GM2 gangliosidosis. *Neurobiol Dis*. 2020 Feb;134:104667. doi: 10.1016/j.nbd.2019.104667. PMID: 31682993.
11. Frati G, Luciani M, Meneghini V, De Cicco S, Ståhlman M, Blomqvist M, Grossi S, Filocamo M, Morena F, Menegon A, Martino S, **Gritti A**. Human iPSC-based models highlight defective glial and neuronal differentiation from neural progenitor cells in metachromatic leukodystrophy. *Cell Death Dis*. 2018 Jun 13;9(6):698. doi: 10.1038/s41419-018-0737-0. PMID: 29899471
12. Mazzara PG, Massimino L, Pellegatta M, Ronchi G, Ricca A, Iannielli A, Giannelli SG, Cursi M, Cancellieri C, Sessa A, Del Carro U, Quattrini A, Geuna S, **Gritti A**, Taveggia C, Broccoli V. Two factor-based reprogramming of rodent and human fibroblasts into Schwann cells. *Nat Commun*. 2017 Feb 7;8:14088. doi: 10.1038/ncomms14088. PMID: 28169300
13. Meneghini V, Frati G, Sala D, De Cicco S, Luciani M, Cavazzin C, Paulis M, Mentzen W, Morena F, Giannelli S, Sanvito F, Villa A, Bulfone A, Broccoli V, Martino S, **Gritti A**. Generation of Human Induced Pluripotent Stem Cell-Derived Bona Fide Neural Stem Cells for Ex Vivo Gene Therapy of Metachromatic Leukodystrophy. *Stem Cells Transl Med*. 2017 Feb;6(2):352-368. doi: 10.5966/sctm.2015-0414. PMID: 28191778
14. Ricca A, **Gritti A**. Perspective on innovative therapies for globoid cell leukodystrophy. *J Neurosci Res*. 2016 Nov;94(11):1304-17. doi: 10.1002/jnr.23752. Review. PMID: 27638612.
15. Meneghini V, Lattanzi A, Tiradani L, Bravo G, Morena F, Sanvito F, Calabria A, Bringas J, Fisher-Perkins JM, Dufour JP, Baker KC, Doglioni C, Montini E, Bunnell BA, Bankiewicz K, Martino S, Naldini L, **Gritti A**. Pervasive supply of therapeutic lysosomal enzymes in the CNS of normal and Krabbe-affected non-human primates by intracerebral lentiviral gene therapy. *EMBO Mol Med*. 2016 May;8(5):489-510. doi: 10.15252/emmm.201505850. Print 2016 May. PMID: 27025653
16. Ricca A, Rufo N, Ungari S, Morena F, Martino S, Kulik W, Alberizzi V, Bolino A, Bianchi F, Del Carro U, Biffi A, **Gritti A**. Combined gene/cell therapies provide long-term and pervasive rescue of multiple pathological symptoms in a murine model of globoid cell leukodystrophy. *Hum Mol Genet*. 2015 Jun 15;24(12):3372-89. doi: 10.1093/hmg/ddv086. PMID: 25749991
17. Lattanzi A, Salvagno C, Maderna C, Benedicenti F, Morena F, Kulik W, Naldini L, Montini E, Martino S, **Gritti A**. Therapeutic benefit of lentiviral-mediated neonatal intracerebral gene therapy in a mouse model of globoid cell leukodystrophy. *Hum Mol Genet*. 2014 Jun 15;23(12):3250-68. doi: 10.1093/hmg/ddu034. PMID: 24463623.

RESEARCH FUNDING

Active

- **2022-2025** *Fondazione Telethon TTAGD0222TT*. Exploiting novel gene therapy platforms and human-based pre-clinical models to understand biology and advance treatment of genetic neurodegenerative and demyelinating diseases. **Role: P.I.**
- **2022-2024** *Bespoke Gene Therapy Consortium (BGTC) FNIH RFP NUMBER: 2022-BGTC003*. Investigating Innate Sensing and Antiviral Restriction of AAV vectors in the Human Central Nervous System. **Role: Co-P.I.** (P.I.: A. Kajaste-Rudnitski)
- **2023-2025** *European Leukodystrophy Association (ELA) ELA 2022-009C2*. Development of editing technologies to treat Alexander's disease. **Role: P.I.**
- **2023-2025** *European Leukodystrophy Association (ELA) ELA 2022-006C2*. Liver-directed gene therapy with enhanced-bioavailability transgenes to treat nervous system pathology in globoid cell leukodystrophy. **Role: co-PI** (P.I. A. Cantore).

Completed

- **2020-2023** *European Joint Programme on Rare Diseases (EJP RD)*. Exploring neuron-glia interactions in leukodystrophies using human iPSC-based models: implication for therapy (NG4Leuko). **Role: Responsible of Research Unit**
- **2022-2023** *Vaincre les Maladies Lysosomales (VML)*. Dissecting the post-translation modifications of Arylsulfatase A (ARSA) in human myeloid cells: relevance for hematopoietic stem cell GT in Metachromatic Leukodystrophy. **Role: P.I.**
- **2020-2022** *European Leukodystrophy Association (ELA) ELA 2019-015I2*. Development of chimeric lysosomal enzymes with improved bioavailability to advance gene therapy strategies for globoid cell leukodystrophy. **Role: P.I.**
- **2021-2022** *European Leukodystrophy Association (ELA) ELA 2020-011I2*. Evaluating the mechanisms of macrophage/microglia-mediated enzymatic cross-correction of human MLD neurons and glial cells in vitro. **Role: P.I.**
- **2018-2021** (extended to 2023) *Italian Ministry of Health RF-2016-02362404*. Exploiting targeted epigenetic editing to increase efficiency and safety of oligodendroglial progenitor cell generation from human iPSC: implications for cell therapy of leukodystrophies. **Role: P.I.**
- **2016-2021** *Fondazione Telethon TGT16D02*. Lysosomal Storage Disorders: Modelling the disease complexity to refine gene/cell therapy treatment strategies. **Role: P.I.**

Members of A. Gritti's lab have been awarded with fellowships/grants from:

- Fondazione U. Veronesi Post-doctoral Fellowships 2016 (A. Ricca)
- Fondazione Centro San Raffaele Post-doctoral Fellowship 2018 (E. Mangiameli) and 2019 (F. Cascino)
- Italian Ministry of Health (GR-2019-12368930 to V. Meneghini; GR-2019-12369357 to A. Ricca)
- Marie Skłodowska-Curie Actions (2020-2022 H2020-MSCA-IF-2019 to V. Meneghini)
- US Department of Defense (FY21 MS Research Program Early Investigator Research Award 2021 to M. Luciani).

Milan, 06.05.2024

Angela Gritti

