Rigoni, Michela Ph.D.

Associate Professor of Pathology

EDUCATION/TRAINING

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| University of Padova, Italy | Degree in Biological Sciences | 1994-2000 |
| University of Padova, Dept. of Biomedical Sciences | PhD in Cellular and molecular Biology and Pathology | Nov 2000-Oct 2003 |
| University of Padova, Dept. of Biomedical Sciences | Post-doctoral training | Nov 2003-Nov 2008 |
| University of Padova, Dept. of Biomedical Sciences | Assistant Professor | Dec 2008- Feb 2021 |
| University of Padova, Dept. of Biomedical Sciences | Associate Professor | Mar 2021-present |

i) During my Master thesis in Biological Sciences (1999-2000) I worked on Clostridial neurotoxins, in particular BoNT/A and TeNT, and clarified the role of specific residues of their light chains in their enzymatic activity (refs 37-40).

ii) During my PhD (2000-2003) and my post-doc training (2004-2008), I focused on a class of presynaptic neurotoxins from Elapid snakes endowed with PLA2 activity, to understand their mechanism of action on neurons in culture and at the NMJ. I discovered that, by cleaving phospholipids of the presynaptic plasma membrane, these toxins generate lysophospholipids and fatty acids that alter the energetics of the presynaptic membrane, thus affecting its disposition to bend and fuse with synaptic vesicles. Their accumulation induces conformational changes in the lipid bilayer, thus favoring the exocytosis of vesicles that are in a hemi-fused state, and inhibiting vesicle retrieval, eventually leading to unbalanced exo-excytosis. These results deserved a Perspective in Science by Zimmemberg and Chernomoridik, pioneers in the study of membrane fusion. Moreover, by altering plasma membrane permeability to calcium, they induce a toxic calcium influx within nerve terminals. In turn, this triggers nerve terminal degeneration and paralysis of the neuromuscular junction (NMJ) (refs 22, 25-36).

iii) Since 2009, I expanded my interests from basic to more translational neuroscience. I exploited my knowledge on neurotoxins to set up an innovative and powerful experimental approach for the neuroregeneration field. The neuroparalysis induced by the animal neurotoxins I have been studying for a long time is fully reversible: indeed, in a few days, the NMJ recovers functionally both in mice and humans, making these toxins a powerful tool to study within a short time window the molecular mechanisms underlying peripheral nerve regeneration following an acute degeneration. I identified hydrogen peroxide produced by mitochondria of injured neurons as a major signaling molecule driving SC activation. Moreover, by combining transcriptomics, electrophysiology and imaging, I am currently investigating the cross-talk taking place at the murine NMJ between damaged nerve terminals, PSCs and the muscle, with the aim of identifying molecules and pathways promoting nerve terminal recovery of function to be tested in different peripheral neuropathies, in a therapeutic perspective. By this approach, I recently I found that the CXCL12α-CXCR4 and melatonin-MT1 signaling axes are crucial for successful peripheral nerve terminal regeneration following acute forms of nerve injuries. I am trying to translate this knowledge to chronic neurodegenerative conditions, by testing the impact of the stimulation of these signaling axes in disease progression in different mouse models of ALS (refs 1-20).

**Honors and awards:**

Highlight in Science mag on Stazi et al, PLOS Negl. Trop. Dis. 14, e0008547 (2020).

Editor's Choice: Leslie K. Ferrarelli. Summoning Schwann cells for neuromuscular recovery. Science Signalling (2015) 8, Issue 364, p. ec35 DOI: 10.1126/scisignal.aaa9059 for the paper Duregotti et al., (2015) Proc Natl Acad Sci USA. 2015 Jan 20. pii: 201417108.

Best poster prize at the World IST meeting in Glasgow (2006): "Calcium influx and mitochondrial alterations at synapses exposed to snake neurotoxins or their phospholipid hydrolysis products".
Perspective by Zimmerberg and Chernomordik published in Science (2005), 310:1626-1627 as comment of the paper by Rigoni et al., (2005) Science 310, 1678-1680.
Patent n° 05015645.4-: "Products for topical application comprising lysophospholipids and fatty acids" (19.07.2005).

**Professional Activities and Memberships**

Reviewer *(ad hoc):* Experimental Neurology, Brain Research, Toxins, Cellular Microbiology, Biomaterials, Journal of Neurochemistry, Cellular and Molecular Life Sciences, Scientific Reports, Frontiers in Cellular Neurosciences, International Journal of Molecular Sciences, Journal of Musculoskeletal Disorders and Treatments, Glia, Cells, The Faseb Journal, Journal of Clinical Medicine, Journal of Pineal Research, Biomedicines, Journal of the Peripheral nervous system.
Memberships: Center of Myology (CIR-Myo) University of Padua, SiTOX (Italian Society of Toxicology), SIPMeT (Italian society of Pathology and Translational Medicine), INA (International Neurotoxin Association)

Nov 2023-present Member of the Third Mission Committee of the Dept. of Biomedical Sciences, University of Padua
July 2022-present Member of the Governing Board of the Myology Centre - CIR-Myo - University of Padua
2019-2023 Member of the Scientific and Resources Committee of the Dept. of Biomedical Sciences, University of Padua
2015-present Member of the PhD Course in Biomedical Sciences, University of Padua
2009-2014 Member of the PhD Course in Biosciences and Biotechnologies, Cellular Biology curriculum, University of Padua

2017 Conference Organizer, Chair and Speaker at the XIII European Meeting on Glial Cell Function in Health and Disease. Lecture: "Motor axon-perisynaptic Schwann cells cross talk at the neuromuscular junction during neurodegeneration." 2017, July 8 –11 Edinburgh, UK.

Guest Editor for the Journal *Cells* of the Special Issue: 'Unveling axon-glia communication in health and disease'. https://www.mdpi.com/journal/cells/special_issues/CZBX79EX22

**Major scientific collaborations:**
Prof. G Sorarù (Clinical Neurology, Dept. of Neuroscience, University of Padua, Italy). Peripheral nerve regeneration in ALS.
Dr. G Viero (Neuromuscular disorders, National Research Council, Institute of Biophysics, Trento, Italy). Next generation sequencing on polysomal RNA.
Prof. CJ Chang (Dept. of Chemistry, University of California, Berkeley, USA). Tools to detect hydrogen peroxide in living cells.
Prof. N Yuki (Dept. of Neurology, Mishima Hospital, Niigata, Japan). Anti-ganglioside antibodies related to GBS autoimmune neuropathies.
Prof. K Jalink (Division of Cell Biology, The Netherlands Cancer Institute, Amsterdam, The Netherlands). Probes for cAMP detection in cells.
Dr. C Mazzanti (Head of Genomics Section, Science Pisa Foundation, Pisa, Italy). Next generation sequencing of murine neuromuscular junctions.
Dr. M Murgia and Prof. M Mann (Dept. of Proteomics and Signal Transduction, Max Planck Institute of Biochemistry, Munich, Germany). NMJ proteomics.
Prof. G Schiavo (Molecular Neuropathobiology, UCL, Institute of Neurology, London, UK). Axonal transport in peripheral nerve regeneration.
Prof. M Mongillo and Dr. T Zaglia (Heart Neurophysiology, Dept. of Biomedical Sciences, University of Padua, Italy). Schwann cells physiology in the heart.
Dr. A Mattarei (Organic Chemistry, Dept. of Pharmaceutical and Pharmacological Sciences, University of Padua, Italy). CXCR4 agonists and peripheral nerve regeneration.
Prof. M Solimena (Max Planck Institute of Molecular Cell Biology and Genetics, Dresden, Germany). Melatonin receptors at the neuromuscular junction.
Prof. R Jockers (Université de Paris, Institut Cochin, CNRS, INSERM, Paris, France). Melatonin receptors at the neuromuscular junction.
Dr. C Bendotti and Dr Giovanni Nardo (Laboratory of Molecular Neurobiology, Dept. of Neuroscience, Milan, Italy). The CXCL12-CXCR4 axis in ALS.

Dr. V Bonetto (Laboratory of Translational Biomarkers, Dept. of Biochemistry and Molecular Pharmacology, Mario Negri Institute, Milan, Italy). The CXCL12α-CXCR4 axis in a FUS model of ALS.
Dr. M Basso (Laboratory of Transcriptional Neurobiology, Dept. of Cellular, Computational and Integrative Biology CIBIO, University of Trento, Trento, Italy). The CXCL12α-CXCR4 axis in a TDP43 mouse model of ALS.
Dr. C Corona (Istituto Zooprofilattico Sperimentale del Piemonte, Liguria e Valle d'Aosta, Turin, Italy). The CXCL12α-CXCR4 axis in swine models of ALS.
Dr. L Murray (Centre for Discovery Brain Sciences, College of Medicine and Veterinary Medicine, University of Edinburgh, UK). The CXCL12α-CXCR4 axis in a mouse model of SMA.
Dr. K Lefkimmiatis and Dr. G Di Benedetto (Foundation for Advanced Biomedical Research, Veneto Institute of Molecular Medicine, Padua, Italy). CXCR4 and cAMP signaling in neurons.
Dr. A Urciuolo (Department of Molecular Medicine, University of Padova, Italy). iPSCs-derived MNs and CXCR4.
Dr Roberta Schellino and Prof Marina Boido (Neuroscience Institute Cavalieri Ottolenghi, University of Torino, Italy).The CXCL12α-CXCR4 axis in a mouse model of ALS
Dr Letizia Marvaldi (Neuroscience Institute Cavalieri Ottolenghi, University of Torino, Italy). Regeneration of sensory neurons.

**Publications**


1. Negro S, Montecucco C, Rigoni M. Extra-pineal melatonin in perisynaptic Schwann cell–muscle fiber cross talk at the regenerating neuromuscular junction. Neural Reg Res (Invited Perspective, accepted for publication on 2024, Nov.18)
2. D'Este G, Fabris F, Stazi M, Baggio C, Simonato M, Megighian A, Rigoni M, Negro S, Montecucco C. Agonists of melatonin receptors strongly promote the functional recovery from the neuroparalysis induced by neurotoxic snakes. PLoS Negl Trop Dis. 2024 Jan 8;18(1):e0011825
3. Negro S, Lauria F, Stazi M, Tebaldi T, D'Este G, Pirazzini M, Megighian A, Lessi F, Mazzanti CM, Sales G, Romualdi C, Fillo S, Lista F, Sleigh JN, Tosolini AP, Schiavo G, Viero G, Rigoni M. Hydrogen peroxide induced by nerve injury promotes axon regeneration via connective tissue growth factor. Acta Neuropathol Commun. 2022 Dec 25;10(1):189.
4. Negro S, Stazi M, Rigoni M, Megighian A. Neurotransmission Recovery by Melatonin Measured by CMAP. Methods Mol Biol. 2022;2550:413-423.
5. Stazi M, Fabris F, Fernández J, D'Este G, Rigoni M, Megighian A, Gutiérrez JM, Lomonte B, Montecucco C. Recovery from the Neuroparalysis Caused by the Micrurus nigrocinctus Venom Is Accelerated by an Agonist of the CXCR4 Receptor. Toxins (Basel). 2022 Aug 2;14(8):531
6. D'Este G, Stazi M, Negro S, Megighian A, Lista F, Rossetto O, Montecucco C, Rigoni M, Pirazzini M. Latrotoxin-Induced Neuromuscular Junction Degeneration Reveals Urocortin 2 as a Critical Contributor to Motor Axon Terminal Regeneration. Int J Mol Sci. 2022 23(3):1186.
7. Negro S, Pirazzini M, Rigoni M. Models and methods to study Schwann cells. J Anat. 2022.
8. Stazi M, Negro S, Megighian A, D'Este G, Solimena M, Jockers R, Lista F, Montecucco C, Rigoni M. Melatonin promotes regeneration of injured motor axons via MT1 receptors. J Pineal Res. 2021 Jan;70(1):e12695.
9. Stazi M, D'Este G, Mattarei A, Negro S, Lista F, Rigoni M, Megighian A, Montecucco C. An agonist of the CXCR4 receptor accelerates the recovery from the peripheral neuroparalysis induced by Taipan snake envenomation. PLoS Negl Trop Dis. 2020 Sep 8;14(9):e0008547.
10. Rigoni M and Negro S. Signals orchestrating peripheral nerve repair. Cells 2020, 9, 1768. Review.
11. Zanetti G, Negro S, Megighian A, Mattarei A, Lista F, Fillo S, Rigoni M, Pirazzini M, Montecucco C. A CXCR4 receptor agonist strongly stimulates axonal regeneration after damage. Ann Clin Transl Neurol. 2019 6(12):2395-2402.
12. Negro S, Zanetti G, Mattarei A, Valentini A, Megighian A, Tombesi G, Zugno A, Dianin V, Pirazzini M, Fillo S, Lista F, Rigoni M, Montecucco C. An Agonist of the CXCR4 Receptor Strongly Promotes Regeneration of Degenerated Motor Axon Terminals. Cells. 2019 Sep 30;8(10).
13. Negro S, Stazi M, Marchioretto M, Tebaldi T, Rodella U, Duregotti E, Gerke V, Quattrone A, Montecucco C, Rigoni M, Viero G. Hydrogen peroxide is a neuronal alarmin that triggers specific RNAs, local translation of Annexin A2, and cytoskeletal remodeling in Schwann cells. RNA. 2018 Jul;24(7):915-925.
14. Rigoni, M., Montecucco, C. (2017) Animal models for studying motor axon terminal paralysis and recovery. Journal of Neurochemistry, 142, pp. 122-129. Review.
15. Negro, S., Lessi, F., Duregotti, E., Aretini, P., La Ferla, M., Franceschi, S., Menicagli, M., Bergamin, E., Radice, E., Thelen, M., Megighian, A., Pirazzini, M., Mazzanti, C.M., Rigoni, M., Montecucco, C. (2017) CXCL12α/SDF-1 from perisynaptic Schwann cells promotes regeneration of injured motor axon terminals. EMBO Molecular Medicine, 9 (8), pp. 1000-1010.
16. Rodella U, Negro S, Scorzeto M, Bergamin E, Jalink K, Montecucco C, Yuki N, Rigoni M. (2017) Schwann cells are activated by ATP released from neurons in an in vitro cellular model of Miller Fisher syndrome. Dis Model Mech. 10:597-603.

17. Rodella U, Scorzeto M, Duregotti E, Negro S, Dickinson BC, Chang CJ, Yuki N, Rigoni M, Montecucco C (2016) An animal model of Miller Fisher syndrome: Mitochondrial hydrogen peroxide is produced by the autoimmune attack of nerve terminals and activates Schwann cells. Neurobiol Dis. 96:95-104.
18. Negro S, Bergamin E, Rodella U, Duregotti E, Scorzeto M, Jalink K, Montecucco C, Rigoni M (2016) ATP Released by Injured Neurons Activates Schwann Cells. Front Cell Neurosci. 10:134.
19. Duregotti E, Zanetti G, Scorzeto M, Megighian A, Montecucco C, Pirazzini M, Rigoni M (2015) Snake and Spider Toxins Induce a Rapid Recovery of Function of Botulinum Neurotoxin Paralysed Neuromuscular Junction. Toxins 7:5322-36.
20. Duregotti E, Negro S, Scorzeto M, Zornetta I, Dickinson BC, Chang CJ, Montecucco C, Rigoni M (2015) Mitochondrial alarmins released by degenerating motor axon terminals activate perisynaptic Schwann cells. Proc Natl Acad Sci U S A 2015 Feb 3;112(5):E497-505.
21. Megighian, A., Zordan, M., Pantano, S., Scorzeto, M., Rigoni, M., Zanini, D., Rossetto, O., Montecucco C (2013) Evidence for a radial SNARE super-complex mediating neurotransmitter release at the Drosophila neuromuscular junction. J Cell Sci 126:3134-3140.
22. Duregotti E, Tedesco E, Montecucco C, Rigoni M (2013) Calpains participate in nerve terminal degeneration induced by spider and snake presynaptic neurotoxins. Toxicon 64:20-28.
23. Rossetto O, Pirazzini, M., Bolognese, P., Rigoni, M., Montecucco, C. (2011). An update on the mechanism of action of tetanus and botulinum neurotoxins. Acta Chimica Slovenica 58, 702-707. Review.
24. Megighian, A., Scorzeto, M., Zanini, D., Pantano, S., Rigoni, M., Benna, C., Rossetto, O., Montecucco, C., and Zordan, M. (2010). Arg206 of SNAP-25 is essential for neuroexocytosis at the Drosophila melanogaster neuromuscular junction. J Cell Sci 123, 3276-3283.
25. Paoli, M., Rigoni, M., Koster, G., Rossetto, O., Montecucco, C., and Postle, A.D. (2009). Mass spectrometry analysis of the phospholipase A(2) activity of snake pre-synaptic neurotoxins in cultured neurons. J Neurochem 111, 737-744.
26. Montecucco, C., Rossetto, O., Caccin, P., Rigoni, M., Morbiato, L., Carli, L., Muraro, L., and Paoli, M. (2008). Different mechanisms of inhibition of nerve terminals by botulinum and snake presynaptic neurotoxins. Toxicon 54, 561-564. Review.
27. Tedesco, E.*, Rigoni, M.*, Caccin, P., Grishin, E., Rossetto, O., and Montecucco, C. (2008). Calcium overload in nerve terminals intoxicated by alpha-latrotoxin and snake PLA2 neurotoxins. Toxicon 54, 138-144.* these authors contributed equally to the work.
28. Rigoni, M., Paoli, M., Milanesi, E., Caccin, P., Rasola, A., Bernardi, P., and Montecucco, C. (2008) Snake PLA2 neurotoxins enter neurons, bind specifically to mitochondria and open their transition pores. J Biol Chem 283, 34013-34020.
29. Rigoni, M., Pizzo, P., Schiavo, G., Weston, A.E., Zatti, G., Caccin, P., Rossetto, O., Pozzan, T. and Montecucco, C. (2007) Calcium influx and mitochondrial alterations at synapses exposed to snake neurotoxins or their phospholipid hydrolysis products. J Biol Chem 282, 11238-11245.
31. Megighian, A., Rigoni, M., Caccin, P., Zordan, M.A. and Montecucco, C. (2007) A lysolecithin/fatty acid mixture promotes and then blocks neurotransmitter release at the Drosophila melanogaster larval neuromuscular junction. Neurosci Lett 416, 6-11.
32. Caccin, P., Rigoni, M., Bisceglie, A., Rossetto, O. and Montecucco, C. (2006) Reversible skeletal neuromuscular paralysis induced by different lysophospholipids. FEBS Lett 580, 6317-6321.
33. Rossetto, O., Morbiato, L., Caccin, P., Rigoni, M. and Montecucco, C. (2006) Presynaptic enzymatic neurotoxins. J Neurochem 97, 1534-1545. Review.
34. Rigoni, M., Caccin, P., Gschmeissner, S. , Rossetto, O., Schiavo, G. and Montecucco, C. (2005) Equivalent effects of snake PLA2 neurotoxins and lysophospholipid-fatty acid mixtures. Science 310, 1678-1680.
35. Bonanomi, D., Pennuto, M., Rigoni, M., Rossetto, O., Montecucco, C. and Valtorta, F. (2005) Taipoxin induces synaptic vesicle exocytosis and disrupts the interaction of synaptophysin I with VAMP2. Mol Pharmacol 67, 1901-1908.
36. Rigoni, M., Schiavo, G., Weston, A., Caccin, P., Allegrini, F., Valtorta, F., Pennuto, M., Montecucco, C. and Rossetto, O. (2004). Snake presynaptic neurotoxins with phospholipase A2 activity induce punctate swellings of neurites and exocytosis of synaptic vesicles. J Cell Sci 117, 3561-3570
37. Caccin, P., Rigoni, M., Bisceglie, A., Rossetto, O. and Rossetto, O., Rigoni, M., Montecucco, C. (2004). Different mechanism of blockade of neuroexocytosis by presynaptic neurotoxins. Toxicol Lett 149, 91-101.
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39. Rigoni M, Caccin P, Johnson EA, Montecucco C, Rossetto O. Site-directed mutagenesis identifies active-site residues of the light chain of botulinum neurotoxin type A. Biochem Biophys Res Commun. 2001 Nov 16;288(5):1231-.7
40. Rossetto, O., Caccin, P., Rigoni, M., Tonello, F., Bortoletto, N., Stevens, R.C., Montecucco, C. (2001). Active-site mutagenesis of tetanus neurotoxin implicates TYR375 and GLU271 in metalloproteolytic activity. Toxicon 39, 1151-1159.