

BIOGRAPHICAL SKETCH

NAME: Maura FRANCOLINI

eRA COMMONS USER NAME (credential, e.g., agency login): n.a.

POSITION TITLE: Associate Professor at Università degli Studi di Milano, Milan - Italy

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Università degli Studi di Milano, Milan - Italy	MSc.	02/1990	Developmental Biology
Università degli Studi di Milano, Milan - Italy	Post-graduate fellow	1991	Developmental Biology
National Research Council (CNR) - Institute of Biomedical Technologies, Rome – Italy	Research fellow	1994	Reproductive and developmental biology, transgenesis
Università degli Studi di Milano, Milan - Italy	Post-doctoral fellow	1995	Cell biology
University of Oslo – Norway	Visiting researcher	05-07/1997	Neuroscience
University of Oslo – Norway	Visiting researcher	10-12/1998	Neuroscience
Università degli Studi di Verona, Verona - Italy	Post-doctoral fellow	01/2000	Neuroscience
King Abdullah University of Science and Technology – Thuwal -Saudi Arabia	Visiting researcher	05-07/2016	Neuroscience
Università degli Studi di Milano, Milan - Italy	Research Technologist	10/2017	Imaging/cell biology/neuroscience
Università degli Studi di Milano, Milan - Italy	Associate Professor	To date	Neuroscience/cell biology

A. Personal Statement

I have a strong background in neuroscience and in the cell biology of the synapse, with a specific expertise in optical and electron microscopy imaging of these structures. My research includes the study of the architecture of peripheral and central synapses in animal models of neurodevelopmental disorders such as intellectual disability (syndromic and non-syndromic), and neurodegenerative disorders such as Amyotrophic Lateral Sclerosis (ALS). I also have extensively studied, at the ultrastructural level, the architecture of intracellular organelles that were found altered in cells exposed to different experimental paradigms and from ALS patients and models, namely mitochondria and endoplasmic reticulum.

Cell and neuron biology, when explored with imaging techniques, often require the combined use of different technologies (i.e. fluorescence and electron microscopy) and set-up especially when correlative approaches are involved. Over the past few years we are increasingly developing and using correlative microscopy protocols (Rodighiero S, Torre B, Sogne E, Ruffilli R, Cagnoli C, **Francolini M**, Di Fabrizio E, and Falqui A. (2015) Correlative Scanning Electron and Confocal Microscopy Imaging of Labeled Cells coated by Indium-Tin-Oxide. *Micr. Res. and Tech.* 78(6).433-443 - Benedetti L, Sogne E, Rodighiero S, Marchesi D, Milani P, **Francolini M**. (2014) Customized patterned substrates for highly versatile correlative light-scanning electron microscopy. *Sci Rep.* 2014 Nov 13;4:7033. doi: 10.1038/srep07033) and, presently, most of our studies on the characterization and study of experimental models of neurodevelopmental disorders rely on correlative studies aiming at the definition, at the nanometer scale, of the structure of neurons, neurites and dendritic spines in type-identified (excitatory or inhibitory) genetically modified neurons which express fluorescent proteins together with the mutant gene of interest. These sparse neurons, within specific rodent brain areas (i.e. hippocampus, somatosensory or prefrontal cortex), are recognized thanks to the expression of the fluorescent protein, their position is defined in space (x, y, z axis) and they are further analyzed taking advantage a new electron microscopy approaches as volume electron microscopy (vEM) through serial block face scanning electron microscopy (SBF_SEM). Recording of the spatial coordinates of selected neurons in brain vibratome sections is achieved through Near InfraRed Branding (NIRB) with a two photon microscope (2P). The use of the 2P system installed at the National Imaging Facility at Human Technopole will be functional and extremely relevant to pursue our research objectives.

B. Positions, Scientific Appointments, and Honors

- **From 02/2000 to 10/2017:** Research Technician, Head of the Optical and Electron Microscopy Unit –Dept. of Medical Biotechnology and Translational Medicine - Università degli Studi di Milano, Milan – Italy
- **From 05/2009 to 12/2015:** Referent scientist of the Cellular Imaging Platform - Filarete Foundation for Bioscience and innovation, Milan – Italy
- **From 05/2016 to 07/2016:** Visiting researcher - King Abdullah University of Science and Technology (KAUST) - Thuwal - Kingdom of Saudi Arabia
- **From 10/2016 to 10/2017:** Adjunct Professor of Applied Pharmacology to Biotechnology - Università degli Studi di Milano, Milan – Italy
- **From 11/2017 - present:** Associate Professor of Applied Biology - Università degli Studi di Milano, Milan – Italy
- **From 2011 to 2017:** Member of the Institute of Neuroscience of the Italian National Research Council (CNR)
- **From 2019 – present:** President of The Master Course in Medical Biotechnology and Molecular Medicine – Facoltà di Medicina e Chirurgia, Università degli Studi di Milano

C. Contributions to Science

Defective formation or function of synapses in the central nervous system (CNS) during development results in disorders of learning and memory, including autism and intellectual disability. These disorders are frequently due to mutations in genes encoding synaptic proteins, involved in cytoskeleton rearrangement, synaptic plasticity, synapse formation and stability or neurotransmission; all aspects affecting either the pre- or the postsynapse structure and function and the number of synapses. In the past four years I devoted much efforts in the characterization of the structure of central synapses of specific areas of the CNS by means of ultrastructural studies on both in vitro and in vivo models of human neurodevelopmental disorders addressing simultaneously all aspects of the synapse anatomy. Together with my collaborators we have developed a *Synapse Toolbox* collecting a list of parameters of the pre- and postsynapse that we systematically analyze and compare between samples and the data we obtain are complemented by data from biochemical assays, electrophysiological recordings and finally behavioral studies. Thanks to these combined

technological approaches we are able to correlate defects in the fine structure of the synapse, differences in protein expression levels and impaired neurotransmission with defects in cognitive functions like learning and memory.

1. Exploiting volume electron microscopy to investigate structural plasticity and stability of the postsynaptic compartment of central synapses. Maiellano G, Scandella L, **Francolini M**. *Front Cell Neurosci*. 2023 Mar 24;17:1153593. doi: 10.3389/fncel.2023.1153593. eCollection 2023. PMID: 37032841
2. Neuronal network activity and connectivity are impaired in a conditional knockout mouse model with PCDH19 mosaic expression. Giansante G, Mazzoleni S, Zippo AG, Ponzoni L, Ghilardi A, Maiellano G, Lewerissa E, van Hugte E, Nadif Kasri N, **Francolini M**, Sala M, Murru L, Bassani S, Passafaro M. *Mol Psychiatry*. 2024 Jun;29(6):1710-1725. doi: 10.1038/s41380-023-02022-
3. Arhgap22 Disruption Leads to RAC1 Hyperactivity Affecting Hippocampal Glutamatergic Synapses and Cognition in Mice. Longatti A, Ponzoni L, Moretto E, Giansante G, Lattuada N, Colombo MN, **Francolini M**, Sala M, Murru L, Passafaro M. *Mol Neurobiol*. 2021 Dec;58(12):6092-6110. doi: 10.1007/s12035-021-02502-x.
4. Marta Prieto, Alessandra Folci, Gwénola Poupon, Sara Schiavi, Valeria Buzzelli, Marie Pronot, Urielle François, Paula Pousinha, Norma Lattuada, Sophie Abelanet, Sara Castagnola, Magda Chafai, Anouar Khayachi, Carole Gwizdek, Frédéric Brau, Emmanuel Deval, **Maura Francolini**, Barbara Bardoni, Yann Humeau, Viviana Trezza & Stéphane Martin (2021) Missense mutation of Fmr1 results in impaired AMPAR-mediated plasticity and socio-cognitive deficits in mice. *Nature Comm*. volume 12, Article number: 1557
5. Colombo MN, Maiellano G, Putignano S, Scandella L, **Francolini M**. (2021) Comparative 2D and 3D Ultrastructural Analyses of Dendritic Spines from CA1 Pyramidal Neurons in the Mouse Hippocampus. *Int J Mol Sci*. 2021 Jan 26;22(3):1188. doi: 10.3390/ijms22031188
6. Mossa A, Pagano J, Ponzoni L, Tozzi A, Vezzoli E, Sciacaluga M, Costa C, Beretta S, **Francolini M**, Sala M, Calabresi P, Boeckers TM, Sala C, Verpelli C. (2021) Developmental impaired Akt signaling in the Shank1 and Shank3 double knock-out mice. *Mol. Psychiatry* doi: 10.1038/s41380-020-00979-x. Online ahead of print.
7. Longaretti A, Forastieri C, Toffolo E, Caffino L, Locarno A, Misevičiūtė I, Marchesi E, Battistin M, Ponzoni L, Madaschi L, Cambria C, Bonasoni MP, Sala M, Perrone D, Fumagalli F, Bassani S, Antonucci F, Tonini R, **Francolini M**, Battaglioli E, Rusconi F. LSD1 is an environmental stress-sensitive negative modulator of the glutamatergic synapse. (2020) *Neurobiol Stress*. 2020 Nov 27;13:100280. doi: 10.1016/j.ynstr.2020.100280.
8. Vezzoli E, Calì C, De Roo M, Ponzoni L, Sogne E, Gagnon N, **Francolini M**, Braidà D, Sala M, Müller D, Falqui A, Magistretti PJ. Ultrastructural Evidence for a Role of Astrocytes and Glycogen-Derived Lactate in Learning-Dependent Synaptic Stabilization. *Cereb Cortex*. 2019 30(4) 2114-2127. doi: 10.1093/cercor/bhz226.
9. Colombo MN, **Francolini M**. (2019) Glutamate at the Vertebrate Neuromuscular Junction: From Modulation to Neurotransmission. *Cells*. 2019 Aug 28;8(9). pii: E996. doi: 10.3390/cells8090996.
10. Gerosa L, **Francolini M**, Bassani S, Passafaro M. (2019) The Role of Protocadherin 19 (PCDH19) in Neurodevelopment and in the Pathophysiology of Early Infantile Epileptic Encephalopathy-9 (EIEE9). *Dev Neurobiol*. 2019 Jan;79(1):75-84. doi: 10.1002/dneu.22654
11. Folci A., Murru L., Vezzoli E., Ponzoni L., Longo F., Moretto E., Gerosa L., Zapata J., Braidà D., Pistillo F., Bähler M., **Francolini M.**, Sala M, Bassani S. (2016) Myosin 9a binds AMPAR and regulates synaptic structure, LTP and cognitive function. *Front Mol Neurosci*. 2016 Jan 20;9:1;
12. Heise C, Taha E, Murru L, Ponzoni L, Cattaneo A, Guarnieri FC, Montani C, Mossa A, Vezzoli E, Ippolito G, Zapata J, Barrera I, Ryazanov AG, Cook J, Poe M, Stephen MR, Kopanitsa M, Benfante R, Rusconi F, Braidà D, **Francolini M**, Proud CG, Valtorta F, Passafaro M, Sala M, Bachi A, Verpelli C, Rosenblum K, Sala C. (2016) eEF2K/eEF2 Pathway Controls the Excitation/Inhibition Balance and Susceptibility to Epileptic Seizures. *Cereb Cortex*. 2016 Mar 21.
13. Zapata J, Moretto E, Hannan S, Murru L, Longatti L, Mazza D, Benedetti L, Fossati M, Heise C, Ponzoni L, Valnegri P, Braidà D, Sala M, **Francolini M**, Hildebrand J, Kalscheuer V, Fanelli F, Sala C, Bettler B, Bassani S, Smart T, and Passafaro M. (2017) Epilepsy and intellectual

disability linked protein Shrm4 interaction with GABABRs shapes inhibitory neurotransmission. *Nature Communications* 6;8:14536. doi: 10.1038/ncomms14536

14. Murru L, Vezzoli E, Longatti A, Ponzoni L, Falqui A, Folci A, Moretto E, Bianchi, V, Braida D, Sala ME, D'Adamo P, Bassani S, **Francolini M** and Passafaro M (2017) AMPA receptors modulation rescues intellectual disability-like phenotype in Tm4sf2-/y mice. *Cerebral Cortex* 1-16 doi: 10.1093/cercor/bhx221

The endoplasmic reticulum is known to transform from a network of branching tubules and cisternae into geometric or stacked membrane arrays (that we termed Organized Smooth ER (OSER)) in response to elevated levels of specific resident components. We investigated, in cultured cell models, the mechanisms underlying this inducible transformation. These mechanisms are important for understanding ER structure and function, as well as general membrane assembly pathways. My specific contribution to the experiments described in the studies listed below is represented by the design and execution of several of the experiments based on optical microscopy techniques and all the experiments based on transmission electron microscopy.

1. Snapp E.L., Hedge R.S., **Francolini M.**, Lombardo F., Colombo S., Pedrazzini E., Borgese N. and Lippincott-Schwartz J. (2003): Formation of stacked ER cisternae by low affinity protein interactions. *J. Cell Biol.*163 (2), 257-269
2. Sprocati T., Ronchi P., Raimondi A., **Francolini M** and Borgese N. (2006): Dynamic and reversible restructuring of the endoplasmic reticulum induced by PDMP in cultured cells. *J. Cell Sci.* 119(15); 3249-3260
3. Borgese N., **Francolini M.** and Snapp E. (2006): Endoplasmic reticulum architecture: Structure in flux. *Curr. Op. Cell Biol.* 18; 1-7
4. Ronchi P., Colombo S., **Francolini M.** and Borgese N. (2008): Transmembrane domain dependent partitioning of membrane proteins within the endoplasmic reticulum. *J. Cell Biol.* 181(1); 105-118
5. Raimondi A., Mangolini A., Rizzardini M., Bendotti C., **Francolini M.**, Borgese N., Cantoni L. and Pietrini G. (2006): *Cell culture models to investigate the selective vulnerability of motoneuronal mitochondria to mutant superoxide dismutase 1 (SOD1) linked to familial amyotrophic lateral sclerosis (ALS)*. *Eur. J. Neurosci.* 24; 387-399;
6. Fasana E, Fossati M, Ruggiano A, Brambillasca S, Hoogenraad CC, Navone F, **Francolini M**, Borgese N (2010) *A VAPB mutant linked to amyotrophic lateral sclerosis generates a novel form of organized smooth endoplasmic reticulum*. *FASEB J.* 2010 24(5): 1419-1430).

The molecular and cellular pathogenetic mechanisms of ALS are not fully identified, and there are no effective cures for ALS patients, although riluzole, the only drug currently approved for ALS treatment, slows the rate of progression and may slightly prolong patient survival through mechanisms that are not completely understood. Skeletal muscle denervation is a key event in this pathology and I investigated in a systematic and quantitative manner, the ultrastructural changes at the neuromuscular junction in the mice expressing the G93A mutant form of SOD1, during disease progression trying to identify precocious subcellular targets of the toxicity of the mutant protein. Surprisingly, in SOD1G93A transgenic mice, muscle fibers denervation was associated to relatively mild aberrant phenotypes in the residual presynaptic terminals thus suggesting a modest contribution of the nerve ending impairments to neuronal damage (Cappello V, Vezzoli E, Righi M, Fossati M, Mariotti R, Bentivoglio M, Pietrini G, **Francolini M.** (2012): *Analysis of neuromuscular junctions and effects of nandrolone administration in a mouse model for ALS*. *Mol Cell Neurosci* 51(1-2): 12-21).

These results prompted us to broaden our field of investigation from the neuromuscular junction alone to motoneuron as a whole and finally to the network of spinal neurons. To do this and in close collaboration with a colleague from my University (Dr. Luca Del Giacco) running the zebrafish facility, we characterized and used zebrafish expressing a mutant form of SOD1 to identify early pathological phenotypes in the nerve-muscle apparatus of this animal. Combining several experimental approaches and tools: behavioral analyses, molecular biology, optical and electron microscopic imaging, the study of the whole organism brought us to the identification of precocious important aberrant phenotypes that involve motoneurons and interneurons hyperexcitability in zebrafish expressing mutant SOD1 and our

results also suggested a possible new mechanism of action of riluzole in controlling mutant SOD1 mediated toxicity (Benedetti L, Ghilardi A, Rottoli E, De Maglie M, Prosperi L, Perego C, Baruscotti M, Bucchi A, Del Giacco L, **Francolini M.** (2016) *INaP selective inhibition reverts precocious inter- and motoneurons hyperexcitability in the Sod1-G93R zebrafish ALS model*. Sci Rep. 15;6:24515).