BIOGRAPHICAL SKETCH

NAME: Maria Teresa Fiorenza

POSITION: Associate Professor of Applied Biology, SSD BIO/13, University "Sapienza" of Rome

EDUCATION and TRAINING

Institution and Location	Degree	Completion date	Field of Study
University "La Sapienza" of Rome, Rome, IT	M.S.	10/1989	Biological Sciences *summa cum laude*
Jackson Laboratory, Bar Harbor, Maine, USA	Pre-doctoral traineeship	03/1990	Biology and Genetics
University of Copenhagen, DK	Pre-doctoral traineeship	07/1994	Biology and Genetics
University "La Sapienza" of Rome, IT	PhD	10/1995	Biotechnology
University "La Sapienza" of Rome, IT	Postdoctoral	12/1997	Developmental Biology
National Institute of Child Health and Development, National NIH, Bethesda, MD, USA	Postdoctoral	10/1999	Developmental Biology

A. Personal Statement

During my scientific career I have acquired a solid expertise in molecular and cellular biology, gene expression analysis, basic and advanced biochemistry, working as pre- and post-doctoral fellow in various laboratories, both in Europe and US.

The wide-ranging training I received allowed me to develop independent thinking skills quite easily and led me to establish novel research activities in my own laboratory. Roughly ten years ago, studies in the field of molecular mechanisms controlling neural development became predominant in my research activity. To address these issues I developed a number of methodological tools and systems, including primary cultures of neural cells and brain slices maintained *ex vivo*. Main issues addressed in my laboratory took a great advantage of genetic mouse models of Alzheimer and Niemann Pick C (NPC) diseases. As for the latter, my expertise with mouse cerebellum steered my attention to the peculiar cerebellar anomalies of this disease. Major findings of this activity are reported in recently peer-review publications, showing that cholesterol dyshomeostasis is responsible of subtle anomalies in developing neurons and glial cells that affect fine motor behavior and largely anticipate the overt appearance of symptoms.

B. Positions and Honors

Positions and Employment

-1992 - 1994: pre-doctoral fellow Dept. of Molecular and Cellular Biology, Copenhagen University, DK

-1995 - 1997: post-doctoral fellow, Dept. of Histology and Medical Embryology, "La Sapienza" University

-1998 - 1999: post-doctoral fellow, Laboratory of Mammalian Genes and Development, National Institute of Child Health and Development, NIH, Bethesda, USA

- 1999 - 2004: Assistant Professor, Department of Psychology, Division of Neuroscience, "La Sapienza" University of Rome, Italy

- 2005 - present: Associate Professor, Department of Psychology, Division of Neuroscience, Sapienza University of Rome, Italy

- ASN 2018-2020 - Qualification to the full professor rank

Honors

- 1992 Marie Curie EU, two-years fellowship.
- 1995 Pasteur Institute - Cenci Bolognetti Foundation, two-years fellowship.
- 1998 Italian National Research Council (CNR), one-year fellowship.
- 1999 Fogarty International, Laboratory of Mammalian Genes and Development, National Institute of Child Health and Development, NIH, Bethesda, USA, one-year fellowship

Other Experience and Professional Membership

- *Member of*: Society for Neuroscience; European Cell Death Organization; Federation of European Neurosciences; Italian Society for Biology and Genetics; Italian Society for Neuroscience.
- *Review Editor***,** Frontiers in Neuroscience since November 2012.
- *Academic Editor*, PLOS ONE since October 2019.
- *Associate Editor,* Frontiers in Molecular Neuroscience, since October 2019.
- *Ad-hoc reviewer for*: Developmental Biology; Journal of Cellular Physiology; Molecular and Cellular Neuroscience; Journal of Cell Science; Neuroscience; PLOS ONE; Journal of Alzheimer Disease, Neurochemical Research, Scientific Reports, BMC Medicine.
- Evaluator for FIRB and SIR project proposals;
- Evaluator in the framework of "Programma Operativo Nazionale Ricerca e Innovazione" 2014-2020 (DP n. 13, 23/11/2020).
- *H2020-MSCA-IF-2020*, Evaluator

Teaching appointments

- January 1998 to October 1999: teacher of "gene cloning and analysis of gene expression patterns" in pre-doctoral courses, NICHD, National Institutes of Health, Bethesda, MD, USA.
- 2000 to present: courses of "Biology", "Foundamentals of Neurobiology and Genetics" and "Neurobiology" at the Faculty of Medicine and Psychology, Sapienza University of Rome;
- 2005 to present: Faculty member of the PhD program of Behavioural Neuroscience, Sapienza University of Rome, mentoring six PhD students.

C. Contribution to Science

1. I have a long-term experience in mammalian embryology and developmental neurobiology. At the beginning of my scientific career I studied the developmental regulation of Heat Shock response in mouse oogenesis and pre-implantation embryo development. In 1992-1994, working at the Dept. of Molecular and Cell Biology of Copenaghen University, I investigated the molecular regulation of heat shock gene transcription factors (HSFs) and identified novel murine HSF1 and HSF2 splice isoforms having additional 66 (mHSF1) and 54 (mHSF2) "in frame" nucleotides, respectively. Results of this study are reported in:

a. **Fiorenza MT**., Farkas T., Dissing M., Kolding D., Zimarino V. (1995). Complex expression of murine heat shock transcription factors. *Nucleic Acids Research*, **23**, 467-74

2. Back to Sapienza University, I continued to work in the same field, developing new micromethods aimed at analyzing molecular processes not approachable by standard techniques, including semiquantitative RT-PCR mRNA determinations on single oocytes/embryos and transcription factor titrations by intranuclear microinjection of competing oligonucleotides in single living cells. Thereafter, using this methodology, I studied the molecular regulation of zygotic genome transcription and embryo blastomere proliferation in the mouse. I also studied the activity of DNA homologous recombination and DNA nonhomologous end joining in dyctiate oocytes and preimplantation embryos. To accomplish these studies I developed a functional assay based on a novel asymmetric PCR measuring the ability of single oocytes and embryos to recombine intranuclearly injected DNA fragments containing a region of homology of various extents at either the 5' or 3' termini.

b. **Fiorenza M.T**., Mangia F. (1998). Quantitative RT-PCR amplification of RNA in single mouse oocytes and preimplantation embryos. *Biotechniques*, **24**, 618-623.
c. Bevilacqua A, **Fiorenza M.T**, Mangia F. (2000). A developmentally regulated GAGA box-binding factor and Sp1 are required for transcription of the hsp70.1 gene at the onset of mouse zygotic genome activation. *Development*, **127**, 1541-1551, **co-first authorship*
d. **Fiorenza MT**, Bevilacqua A, Bevilacqua S, F. Mangia (2001). Growing dictyate oocytes, but not early preimplantation embryos, of the mouse display high levels of DNA homologous recombination by single-strand annealing and lack DNA nonhomologous end joining. *Developmental Biology*, **233**, 214-224
e. Narducci M.G., **Fiorenza M.T**., Kang S-M., Bevilacqua A., Di Giacomo M., Remotti D., Picchio M.C., Fidanza V., Cooper M.D., Croce C.M., Mangia F., Russo G. (2002). TCL1 participates in early embryonic development and is overexpressed in human seminomas. *Proceedings of the National Academy of Sciences of the United States of America*, **99**,

11712-11717, **co-first authorship*
f. **Fiorenza M T**, Torcia S, Canterini S, Bevilacqua S, Narducci M G, Ragone G, Croce C M, Russo G, F., Mangia (2008). TCL1 promotes blastomere proliferation through nuclear transfer, but not direct phosphorylation, of AKT/PKB in early mouse embryos. *Cell Death and Differentiation*, **15**, 420-422.
g. **Fiorenza MT**, Russo G, Narducci MG, Bresin A, Mangia F, Bevilacqua A (2019). Protein kinase Akt2/PKBβ is involved in blastomere proliferation of preimplantation mouse embryos. J Cell Physiol. 2019 Sep 25. doi: 10.1002/jcp.29229. h. **Fiorenza MT** & Rava A (2019). The TCL1 function revisited focusing on metabolic requirements of stemness. Cell Cycle. 2019 Nov;18(22):3055-3063.

3. During a two years post-doctoral position (1998 - 1999) in Dr. Westphal's laboratory at the NIH of Bethesda, I also became well acquainted with the field of the developmental neurobiology. By exploiting the *lhx3* null mutant mice, which display pituitary hypoplasia, I identified genes differentially expressed in the developing pituitary gland of *wild type* and *lhx3* null mutant embryos by subtractive hybridization and library screening. This approach led me to identify several novel genes, among which were *Tsc22d4*, belonging to the family of TGF beta1-stimulated genes. Thereafter, pursuing the functional characterization of this gene I have developed specific tools to investigate neuronal development, with particular reference to the cerebellum.

i. **Fiorenza M.T**., Mukhopadhyay M., Westphal H. (2001). Expression screening for Lhx3 downstream genes identifies Thg-1pit as a novel mouse gene involved in pituitary development. *GENE*, **278**, 125-130.
j. Canterini S, Bosco A, De Matteis V, F. Mangia, **Fiorenza M.T.** (2009). THG-1pit moves to nucleus at the onset of cerebellar granule neurons apoptosis. *Molecular Cellular Neuroscience*, **40**, 249-257

4. More recently, my research interests also included the study of molecular and cellular mechanisms underlying neurodegeneration in Alzheimer disease and few years ago I entered the field of genetic rare disease of lysosomal cholesterol storage. Exploiting genetic mouse model of the Niemann Pick type C (NPC) disease I have characterized the anomalies of cerebellar morphogenesis and the ability of β-cyclodextrin to rescue these anomalies.

m. Nusca S, Canterini S, Palladino G, Bruno F, Mangia F, Erickson RP, **Fiorenza MT** (2014). A marked paucity of granule cells in the developing cerebellum of the Npc1(-/-) mouse is corrected by a single injection of hydroxypropyl-β-cyclodextrin. *Neurobiol Dis*. **70**, 117-26
l. Caporali P, Bruno F, Palladino G, Dragotto J, Petrosini L, Mangia F, Erickson RP, Canterini S, **Fiorenza MT**. (2014) Developmental delay in motor skill acquisition in Niemann-Pick C1 mice reveals abnormal cerebellar morphogenesis. *Acta Neuropathol Commun*., **4**, 94.
n. S Canterini, J Dragotto, A Dardis, S Zampieri, ME De Stefano, F Mangia, RP Erickson, **MT Fiorenza**. (2017) Shortened primary cilium length and dysregulated Sonic hedgehog signaling in Niemann-Pick C1 disease. *Hum Mol Genet*. **26**, 2277-2289
o. **Fiorenza MT**, Moro E, Erickson RP. (2018) The pathogenesis of lysosomal storage disorders: beyond the engorgement of lysosomes to abnormal development and neuroinflammation
Hum Mol Genet. 27(R2):R119-R129
5. Since a couple of years, collaborating with Dr. Kulkarni, Oraxion Therapeutics, I'm involved in the identification and validation of novel β-cyclodextrin-based therapeutics for NPC.
p. Kulkarni A, Caporali P, Dolas A, Johny S, Goyal S, Dragotto J, Macone A, Jayaraman R, **Fiorenza MT**. (2018) Linear Cyclodextrin Polymer Prodrugs as Novel Therapeutics for Niemann-Pick Type C1 Disorder Sci Rep. 8(1):9547. q. Oddi S, Caporali P……**Fiorenza MT** (2019). The endocannabinoid system is affected by cholesterol dyshomeostasis: Insights from a murine model of Niemann Pick type C disease. Neurobiol Dis. 2019 Oct;130:104531.

Ongoing Collaborations
- Dr. **Sergio Oddi**, Sergio Oddi, European Center for Brain Research (CERC)/Santa Lucia Foundation IRCCS, Rome, Italy.
- **Aditya Kulkarni**, Oraxion Therapeutics, Bangalore, India, http://www.oraxiontx.com inventor and provider of the β-CD prodrug;
- Prof. **Robert P Erickson** (RPE), Dept. of Pediatrics, University of Arizona School of Medicine, Tucson, AZ, 85724-5073, US.
- Dr. **Andrea Dardis**, Regional Centre for Rare Diseases, Hospital of Udine, Italy.

Grants
- 2020 Sapienza H2020, “Hypoxic ischemic brain injury pathophysiology: a deeper understanding of hypoxia-resilient neurons and microvasculature modulation for post-cardiac arrest recovery (HIBImod)”; Euro 40.000,00 (PI);
- 2020 Fondazione Telethon, Telethon n. GSP20006_Covid050, “Inactivation of the Niemann Pick C1 protein as a strategy to inhibit SARSCoV2 infection”; Euro 49.980,00 (PI);
- 2019 Ara Parseghian Medical Foundation, “Investigating Niemann Pick C pathophysiology in mouse models”; Euro 20.000,00 (PI);
- 2017 Oraxion Therapeutics donation, “Characterizing the efficacy of a b-cyclodextrin prodrug in Niemann Pick C mouse models; Euro 20000,00 (PI);
- 2016 - Sapienza “Visiting Professor” - Robert Porter Erickson; Euro 5000,00 (PI);
- 2016 – Sapienza “Investigating abnormal cerebellum morphogenesis in Niemann-Pick C 1 disease and the potential of novel therapeutic approaches”; Euro 11000,00 (PI);
- 2013 – Fondazione Telethon, “Enligthening molecular mechanisms of abnormal cerebellum development in mouse models of human Niemann-Pick C 1 disease: the efficacy of hydroxyproplyl-b-cyclodextrin in correcting the phenotype”; Euro 111700,00 (PI);
- 2012 - Sapienza “Grandi e medie attrezzature”; Euro 19000,00 (PI);
- 2012 - Sapienza “Visiting Professor” - Robert Porter Erickson; Euro 8100,00 (PI);
- 2012 - EC FP7 “DevelAge - Pathways common to brain development and ageing”; Euro 110000,00 (Co-PI);
- 2010 - Sapienza “How many roles for TSC22D4 protein in cerebellum granule neurons of the mouse: isoforms' subcellular localization and functional interactions”; Euro 5000,00 (PI);
- 2008 - Sapienza “Caratterizzazione del ruolo funzionale del gene Thg-1pit nella regolazione del bilancio tra proliferazione/differenziamento e apoptosi nei granuli cerebellari del topo”; Euro 6000,00 (PI)
- 2008 - Sapienza “Un approccio molecolare ed elettrofisiologico allo studio dello sviluppo dei circuiti della corteccia cerebellare”; Euro 5000,00 (PI);
- 2008 - Istituto Pasteur - Fondazione Cenci Bolognetti “Molecular regulation of cell proliferation and apoptosis in early embryo blastomeres and granule neuron precursors of the mouse”; Euro 45000,00 (co-PI);

Publications (*last 5 years*)

1. La Rosa P, Petrillo S, **Fiorenza MT**, Bertini ES, Piemonte F. (2020) Ferroptosis in Friedreich's Ataxia: A Metal-Induced Neurodegenerative Disease. Biomolecules 10(11):1551. doi: 10.3390/biom10111551

2. La Rosa P, Petrillo S, Turchi R, Berardinelli F, Schirinzi T, Vasco G, Lettieri-Barbato D, **Fiorenza MT**, Bertini ES, Aquilano K, Piemonte F. (2020) The Nrf2 induction prevents ferroptosis in Friedreich's Ataxia Redox Biol. 38:101791. doi: 10.1016/j.redox.2020.101791.

3. Monti N, Cavallaro RA, Stoccoro A, Nicolia V, Scarpa S, Kovacs GG, **Fiorenza MT**, Lucarelli M, Aronica E, Ferrer I, Coppedè F, Troen AM, Fuso A. (2020) CpG and non-CpG Presenilin1 Methylation Pattern in Course of Neurodevelopment and Neurodegeneration Is Associated With Gene Expression in Human and Murine Brain. Epigenetics 5;1-19. doi: 10.1080/15592294.2020.1722917

4. Erickson RP, Aras S, Purandare N, Hüttemann M, Liu J, Dragotto J, **Fiorenza MT**, Grossman LI. (2020) Decreased Membrane Cholesterol in Liver Mitochondria of the Point Mutation Mouse Model of Juvenile Niemann-Pick C1, *Npc1* ^{nmf164}. *Mitochondrion*, 51, 15-21

5. **Fiorenza MT**, Rava A. (2019) The TCL1 function revisited focusing on metabolic requirements of stemness. *Cell Cycle*,18(22):3055-3063. doi: 10.1080/15384101.2019.1672465.

6. **Fiorenza MT**, Russo G, Narducci MG, Bresin A, Mangia F, Bevilacqua A. Protein kinase Akt2/PKBβ is involved in blastomere proliferation of preimplantation mouse embryos. *J Cell Physiol.* 2019 Sep 25. doi: 10.1002/jcp.29229.

7. Dragotto J, Palladino G, Canterini S, Caporali P, Patil R, **Fiorenza MT**, Erickson RP (2019) Decreased neural stem cell proliferation and olfactionin mouse models of Niemann-Pick C1 disease and the response to hydroxypropyl-β-cyclodextrin. *Journal of Applied Genetics,* 60:357-365. doi.org/10.1007/s13353-019-00517-8

8. Oddi S, Caporali P, Dragotto J, Totaro A, Maiolati M, Scipioni L, Angelucci CB, Orsini C, Canterini S, Rapino C, Maccarrone M, **Fiorenza MT** (2019) The endocannabinoid system is affected by cholesterol dyshomeostasis: Insights from a murine model of Niemann Pick type

C disease. *Neurobiol Dis*. 130:104531. doi: 10.1016/j.nbd.2019.104531.

9. Lucarelli M, Di Pietro C, La Sala G, **Fiorenza MT**, Marazziti D, Canterini S. (2019) Anomalies in Dopamine Transporter Expression and Primary Cilium Distribution in the Dorsal Striatum of a Mouse Model of Niemann-Pick C1 Disease. *Front Cell Neurosci* 13:226. doi: 10.3389/fncel.2019.00226.

10. Dragotto J, Canterini S, Del Porto P, Bevilacqua A, Fiorenza MT (2019) The interplay between TGF-β-stimulated TSC22 domain family proteins regulates cell-cycle dynamics in medulloblastoma cells. *J Cell Physiol*. 234(10):18349-18360. doi: 10.1002/jcp.28468.

11. Bresin A, Ragone G, Cristofoletti C, Arcelli D, Bassi C, Caprini E, **Fiorenza MT**, Helmer Citterich M, Russo G, Narducci MG. (2018) T Cell Leukemia/Lymphoma 1A is essential for mouse epidermal keratinocytes proliferation promoted by insulin-like growth factor 1. *PLoS One* 13:e0204775. doi: 10.1371/journal.pone.0204775.

12. Kulkarni A, Caporali P, Dolas A, Johny S, Goyal S, Dragotto J, Macone A, Jayaraman R and **Fiorenza MT**. (2018) Linear Cyclodextrin Polymer Prodrugs as Novel Therapeutics for Niemann-Pick Type C1 Disorder. *Scientific Reports* 8:9547 doi:10.1038/s41598-018-27926-9

13. **Fiorenza MT**, Moro E, Erickson RP. (2018) The pathogenesis of lysosomal storage disorders: beyond the engorgement of lysosomes to abnormal development and neuroinflammation. *Hum Mol Genet* 27(R2):R119-R129 doi: 10.1093/hmg/ddy155.

14. Pipolo S, Puglisi R, Mularoni V, Esposito V, Fuso A, Lucarelli M, **Fiorenza MT**, Mangia F, Boitani C. (2018) Involvement of sperm acetylated histones and the nuclear isoform of Glutathione peroxidase 4 in fertilization. *J Cell Physiol*. 233:3093-3104

15. Erickson RP, **Fiorenza MT**. (2017) A hopeful therapy for Niemann Pick C diseases *Lancet*, 390 (10104):1720-1721.

16. Cavallaro RA, Nicolia V, **Fiorenza MT**, Scarpa S, Fuso A. (2017) S-Adenosylmethionine and Superoxide Dismutase 1 Synergistically Counteract Alzheimer's Disease Features Progression in TgCRND8 Mice. *Antioxidants* (Basel), Sep 30;6(4).

17. Campus P, Canterini S, Orsini C, **Fiorenza MT**, Puglisi-Allegra S, Cabib S. (2017) Stress-Induced Reduction of Dorsal Striatal D2 Dopamine Receptors Prevents Retention of a Newly Acquired Adaptative Cope Strategy. *Front Pharmacol.* 8:621

18. S Canterini, J Dragotto, A Dardis, S Zampieri, ME De Stefano, F Mangia, RP Erickson, **MT Fiorenza** (2017) Shortened primary cilium length and dysregulated Sonic hedgehog signaling in Niemann-Pick C1 disease. *Hum Mol Genet*. 26: 2277-2289

19. Palladino G, Nicolia V, Kovacs GG, Canterini S, Ciraci V, Fuso A, Mangia F, Scarpa S, **Fiorenza MT**. (2017) Sexually Dimorphic Expression of Reelin in the Brain of a Mouse Model of Alzheimer Disease. *J Mol Neurosci.* 61:359-367

17. Caporali P, Bruno F, Palladino G, Dragotto J, Petrosini L, Mangia F, Erickson RP, Canterini S, **Fiorenza MT**. (2016) Developmental delay in motor skill acquisition in Niemann-Pick C1 mice reveals abnormal cerebellar morphogenesis. *Acta Neuropathol Commun*. 4:94

20. Dardis A, Zampieri S, Canterini S, Newell KL, Stuani C, Murrell JR, Ghetti B, **Fiorenza MT**, Bembi B, Buratti E. (2016) Altered localization and functionality of TAR DNA Binding Protein 43 (TDP-43) in niemann- pick disease type C. *Acta Neuropathol Commun.* 4:52

21. Bresin A, D'Abundo L, Narducci MG, **Fiorenza MT**, Croce CM, Negrini M, Russo G. (2016) TCL1 transgenic mouse model as a tool for the study of therapeutic targets and microenvironment in human B-cell chronic lymphocytic leukemia. *Cell Death Dis.* 7:e2071.

22. Palladino G, Loizzo S, Fortuna A, Canterini S, Palombi F, Erickson RP, Mangia F, **Fiorenza MT**. (2015) Visual evoked potentials of Niemann-Pick type C1 mice reveal an impairment of the visual pathway that is rescued by 2-hydroxypropyl-ß-cyclodextrin. *Orphanet J Rare Dis*.10:133

23. Niceta M, Stellacci E, Gripp KW, Zampino G, Kousi M, Anselmi M, Traversa A, Ciolfi A, Stabley D, Bruselles A, Caputo V, Cecchetti S, Prudente S, **Fiorenza MT**, Boitani C, Philip N, Niyazov D, Leoni C, Nakane T, Keppler-Noreuil K, Braddock SR, Gillessen-Kaesbach G,

Palleschi A, Campeau PM, Lee BH, Pouponnot C, Stella L, Bocchinfuso G, Katsanis N, Sol-Church K, Tartaglia M. (2015) Mutations impairing GSK3-mediated MAF phosphorylation cause cataract, deafness, intellectual disability, seizure and Down syndrome-like facies *Am J Hum Genet*. 96:816-25

24. Mione V, Canterini S, Brunamonti E, Pani P, Donno F, **Fiorenza MT**, Stefano Ferraina (2015). Both COMT Val158Met single nucleotide polymorphism and sex-dependent differences influence response inhibition. *Front Behav Neurosci*. 9:127

25. Dragotto J, Capuozzo E, Fontana M, Curci A, **Fiorenza MT**, Canterini S. (2015) Thiotaurine protects mouse cerebellar granule neurons from potassium deprivation-induced apoptosis by inhibiting the activation of caspase-3. *Adv Exp Med Biol.* 803:513-23

Complete List of Published Work:
https://www.ncbi.nlm.nih.gov/pubmed/?term=Fiorenza+MTD.