BIOGRAPHICAL SKETCH

NAME: Maria Giulia Farace

POSITION TITLE: Honorary Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date MM/YYYY	FIELD OF STUDY
University of Rome La Sapienza, Rome, IT	M.Sc.	1966	Biology
Istituto Superiore di Sanita' (Public Health Service) Rome, IT	Postgraduate	1967-1968	Cellular and Molecular Biology
Laboratory of Cytology and Embryology, ENEA, Rome, IT	Postgraduate	1969-1970	Cellular and Molecular Differentiation
Department of Human Genetics, Prof. Paul Marks Lab.,Columbia University, New York,	Postdoc Fellow	1970-1972	Cellular and Molecular Differentiation
Department of Genetics, Prof. John Bishop Lab., Edinburgh University, Scotland	Postdoc Fellow	1972-1973	Biotechnology: gene cloning and isolation
Department of Pathology and Immunology, Prof. Bernard Mach Lab., University of Geneva, Switzerland	Senior Research Fellow	1973-1975	Molecular Immunology

A. Personal Statement

The research I developed with my group at "Tor Vergata" University was focused on the molecular therapeutic approaches for glioblastoma multiforme (GBM). GBM is one of the most lethal forms of human cancer, characterized by a poor prognosis associated with a median survival of less than 12 months. It exhibits a relentless malignant progression characterized by widespread invasion throughout the brain, resistance to traditional and/or differentiative newer targeted therapeutic approaches. In particular, in the last years we investigated the role of microRNAs (miRNAs) in cancer stem cells (CSC) isolated from GBM patients. Several studies have demonstrated the existence in specific niches of GBM tumor tissue of a small fraction of cells, "cancer stem cells" (CSCs)' that are able to maintain tumor growth and proliferation and to determine tumor relapse. The isolation of CSCs has introduced a new and revolutionary paradigm in cancer therapy representing a primary therapeutic target. The disruption of miRNA

expression patterns has been associated with several examples of human tumorigenesis, making them a novel class of important oncogenes or tumor suppressor genes.

B. Positions and Honors

Academic Appointments:

1973 -1975	Maitre-Assistant, Dpt. of Pathology, Faculty of Medicine University of Geneva
1975 -1982	Research worker, Institute of General Biology, Faculty of Medicine, University of Rome "La Sapienza"
1978 -1982	Lecturer of Biology and Genetics, Faculty of Medicine, University of Rome "La Sapienza"
1982 -1986	Associate Professor of Biology and Genetics, Faculty of Medicine, University of Rome "La Sapienza"
1986 -1988	Full Professor of Biology and Genetics, Faculty of Medicine, University of Reggio Calabria, Italy
1988 -1997	Full Professor of Cellular Physiology, Faculty of Medicine, University of Rome "Tor Vergata"
1993 - 2009	Lecturer of Applied Biology, Faculty of Medicine, "Libero Istituto Campus Biomedico", Rome, Italy
1997 - 2014	Full Professor of Applied Biology, Faculty of Medicine, University of Rome "Tor Vergata", Italy and Director of the Biology Section of the Faculty of Medicine, University of Rome "Tor Vergata"
2004 - 2014	Lecturer of Applied Biology, Faculty of Medicine, University "Nostra Signora del Buon Consiglio" Tirana, Albania
2012 - to present	Lecturer of Applied Biology, English Course of Medicine and Surgery, University of Rome, Italy
2014 - to present	Honorary Professor, Department of Biomedicine and Prevention, Faculty of Medicine, University of Rome "Tor Vergata", Italy

Honors:

1971-72	NATO Fellowship
1973	EMBO long term Fellowship
1977	EMBO short term Fellowship
1980	Invited Visiting Scientist, Department of Pathology University of Geneva, Switzerland
1981-82	Invited Visiting Scientist, Department of Microbiology and Immunology, University of North Carolina, Chapel Hill, USA
1983-84	Invited Visiting Professor, Department of Microbiology and Immunology, University of North Carolina, Chapel Hill, USA
1989	Invited Visiting Professor, University of North Carolina, Chapel Hill, USA
1992-93	Invited Visiting Professor in Molecular Biology, Gladstone Institute for Cardiovascular Diseases, University of California, San Francisco, USA

1990-2001 Research Appointment, Institute of Experimental Medicine CNR (National Research Council, Rome, Italy.

2003-2004 Invited Visiting Professor, Universidad Autonoma de Madrid, Centro de Biologia Severo Ochoa, lab. Prof. Marta Izquierdo, Madrid, Spain.

2004 Collaboration with Dr. Carlo M. Croce, Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA, USA.

C. Contribution to Science

In the last years, my laboratory studied the global miRNome in glioblastoma cell lines and patient samples, thus defining a selection of microRNAs specifically down- or up-regulated in these tumors. Furthermore, we identified $p27^{kip1}$ as a key target molecule of miR-221 and miR-222, the microRNAs that we found to be most overexpressed in tumors (Galardi et al., 2007; le Sage et al., 2007; Mercatelli et al., 2008). The identification of $p27^{kip1}$, a master negative regulator of the cell cycle, as a prominent target of miR-221/222, supported our hypothesis that these microRNAs play an oncogenic role in glioblastoma. We have also characterized the microRNA expression profile in CSCs isolated from GBM patients and more recently we have investigated their role in CSC survival, proliferation, differentiation and chemoresistance, in order to define an appropriate microRNA-based therapy that could, alone or in combination with conventional chemotherapy, contribute to eradication of tumor.

Recently, in collaboration with Prof. Claudia Bagni, we demonstrated that high levels of FMRP (Fragile X Messenger Ribonucleoprotein Protein 1) are correlated with indicators of aggressiveness and invasiveness of different types of cancer as glioblastoma, breast and melanoma (Pedini et al.2022; Lucà et al. 2013; Zalfa et al. 2013; Zalfa et al. 2017).

International Collaborations

Prof. Bernard Mach, Department of Pathology, University of Geneva, Switzerland.
Prof. C.A. Hutchison, Department of Microbiology and Immunology, Curriculum in Genetics, University of North Carolina, Chapel Hill, N.C., U.S.A.
Prof. Paul Marks, Sloan Kettering Memorial Hospital, New York.
Prof. Marta Izquierdo, “Severo Ochoa” Molecular Biology Center, Universitad Autonoma de Madrid, Spain.
Prof. Carlo Croce, Ohio University, Cincinnati, USA.
Prof. Reuven Agami, The Netherlands Cancer Institute, Amsterdam.

National Collaborations

Prof Giulio Maira, Istituto di Neurochirurgia, Università Cattolica del Sacro Cuore, Roma.
Prof Gaetano Finocchiaro, Istituto Neurologico Carlo Besta, Milano.
Prof. Giovanni Barillari, Dip. di Medicina Sperimentale e Scienze Biochimiche, Università di Roma” Tor Vergata”.
Prof. Ruggero De Maria, Dip. Ematologia, Oncologia e Medicina Molecolare, Istituto Superiore di Sanità, Roma.
Prof, Flavio Keller, Laboratorio di Neuroscienze, Università Campus Biomedico, Roma.
Prof. Claudia Bagni, Dip. di Biomedicina e Prevenzione, Università di Roma” Tor Vergata”

D. Research Support (from 2000)

2000-2003. Consiglio Nazionale Ricerche (National Research Council) (CNR) Grants n.CU00.00638 and n.99.01223CT26 for a project entitled “ Costruzione di vettori

retrovirali antiangiogenesi per terapia genica somatica di tumori cerebrali" Role: *Principal Investigator*

2001-2002. Ministero della Sanita' (Ministry of Health) Grant for a project entitled "Sviluppo di vettori retrovirali per la terapia antiangiogenica di tumori cerebrali" Role: *Principal Investigator*

2000–2002. Ministero dell'Università e Ricerca (MIUR) Grant for a project entitled " Approcci innovativi combinati di terapia genica dei gliomi maligni" (PRIN E FIRB grants 2001-2003)Role: *Principal Investigator*

2002 –2004. Ministero della Sanita'. IRCCS Santa Lucia, Grant for a project entitled "Ruolo della reelina nella neurodegenerazione: implicazioni biochimiche e funzionali" Role: *Principal Investigator (U.O. n.5)*

2003-2004. Ministero dell'Università e Ricerca (MIUR) Grant for a project entitled "Recupero della espressione e della funzione di Reelin nel topo reeler". Role: *Principal Investigator*

2003 – 2005. Ministero della Sanità (Ministry of Health) "National Program on Stem Cells" Grant for a project entitled "Engineering neural stem cells for gene therapy of glioblastoma: role of reelin in neural stem cell migration" Role: *Principal Investigator*

2007-2008. I.S.S. Istituto Superiore di Sanità (Italian Public Health Service), Ministry of Health: Italia-USA National Project "MicroRNA and antisense sequences" .Grant for a project entitled "Characterisation of microRNAs expression in subpopulations of glioblastoma multiforme cells". Role: Co-*Principal Investigator*

2007-2008. Ministero dell'Universita' e Ricerca (MIUR) PRIN (National Research Program) Grant for a project entitled "microRNAs role in cell differentiation and tumorogenesis" Role:Co- *Principal Investigator*

2009-2011. I.S.S. Istituto Superiore di Sanità (Italian Public Health Service), Ministry of Health: Italia-USA Project "Role of MicroRNA in Glioblastoma Stem Cells". Grant for a project entitled "MicroRNAs as molecular markers of glioblatoma multiforme". Role: *Principal Investigator*

SELECTED PUBLICATIONS (2005 to present)

Cencelli G, Pacini L, De Luca A, Messia I, Gentile A, Kang Y, Nobile V, Tabolacci E, Jin P, **Farace MG**, Bagni C. *Age-Dependent Dysregulation of APP in Neuronal and Skin Cells from Fragile X Individuals.* ***Cells***. 2023 Feb 27;12(5):758. doi: 10.3390/cells12050758. PMID: 36899894; PMCID: PMC10000963

Pedini G, Buccarelli M, Bianchi F, Pacini L, Cencelli G, D'Alessandris QG, Martini M, Giannetti S, Sasso F, Melocchi V, **Farace MG**, Achsel T, Larocca LM, Ricci-Vitiani L, Pallini R, Bagni C. *FMRP modulates the Wnt signalling pathway in glioblastoma.* ***Cell Death Dis.*** 2022 Aug 18;13(8):719. doi: 10.1038/s41419-022-05019-w. PMID: 35982038; PMCID: PMC9388540.

Zalfa F, Panasiti V, Carotti S, Zingariello M, Perrone G, Sancillo L, Pacini L, Luciani F, Roberti V, D'Amico S, Coppola R, Abate SO, Rana RA, De Luca A, **Farace MG**, Fiers M, Achsel T, Marine JC, Morini S and Bagni C. The Fragile X Mental Retardation Protein regulates tumor invasiveness-related pathways in melanoma cells. ***Cell Death Dis.***, 2017 *8(11), e3169***.**

Galardi S, Savino M, Scagnoli F, Pellegatta S, Pisati F, Zambelli F, Illi B, Annibali D, Beji S, Orecchini E, Alberelli MA, Apicella C, Fontanella RA, Michienzi A, Finocchiaro G**, Farace MG**, Pavesi G, Ciafrè SA, Nasi. "Resetting cancer stem cell regulatory nodes upon MYC inhibition". ***EMBO Rep.*** 2016 Dec;17(12):1872-1889.

Fazi B, Felsani A, Grassi L, Moles A, D'Andrea D, Toschi N, Sicari D, De Bonis P, Anile C, Guerrisi MG, Luca E, **Farace" MG**, Maira G, Ciafré SA, Mangiola A. "The transcriptome and

miRNome profiling of glioblastoma tissues and peritumoral regions highlights molecular pathways shared by tumors and surrounding areas and reveals differences between short-term and long-term survivors". ***Oncotarget.*** 2015 Sep 8;6(26):22526-52.

Luchetti A, Ciafre' SA, Murdocca M, Malgieri A, Masotti A, Sanchez M, **Farace MG**, Novelli G, Sangiuolo F. "A perturbed microRNA expression pattern characterizes embryonic neural stem cells derived from a severe mouse model of Spinal Muscular Atrophy (SMA)" **Int. J. Mol..Sci.** 2015, 16 18312-18327.

Orecchini E, Doria M, Michienzi A, Giuliani E, Vassena L, Ciafrè SA**, Farace MG**, Galardi S. "The HIV-1 Tat protein modulates CD4 expression in human T cells through the induction of miR-222". ***RNA Biol***. 2014;11(4):334-8. doi: 10.4161/rna.28372.

Fazi B, Sicari D, Galardi S. **Farace MG**, Maira G, De BonisP, Anile G, Mangiola A, Ciafre' SA. "An integrated view of the transcriptome and miRNome of glioblastoma and peritumor tissues", ***Anticancer Research*** 34 (10):5865, Oct 2014.

Lucà R, Averna M, Zalfa F, Vecchi M, Bianchi F, La Fata G, Del Nonno F, Nardacci R, Bianchi M, Nuciforo P, Munck S, Parrella P, Moura R, Signori E, Alston R, Kuchnio A, **Farace MG,** Fazio VM, Piacentini M, De Strooper B, Achsel T, Neri G, Neven P, Evans DG, Carmeliet P, Mazzone M, Bagni C." The fragile X protein binds mRNAs involved in cancer progression and modulates metastasis formation. "***EMBO Mol Med.*** 2013 Oct;5(10):1523-36.

Galardi S, Mercatelli N, **Farace MG,** Ciafrè SA. NF-kB and c-Jun induce the expression of the oncogenic miR-221 and miR-222 in prostate carcinoma and glioblastoma cells. ***Nucl. Acids Res***., 2011 39(9):3892-902.

Doria M, Tomaselli S, Neri F, Ciafrè SA, **Farace MG**, Michienzi A, Gallo A. ADAR2 editing enzyme is a novel human immunodeficiency virus-1 proviral factor. ***J Gen Virol.***,2011 92(5):1228-32.

Mercatelli N, Dimauro I,Ciafré SA**, Farace MG**, Caporossi D. AlphaB-crystallin is involved in oxidative stress-protection determined by VEGF in skeletal myoblasts*.* ***Free Radic Biol Med.***, 2010,49: 374-382,

Doria M, Neri F, Gallo A, **Farace MG**, Michienzi A."Editing of HIV-1RNA by double- stranded RNA deaminase ADAR1 stimulates viral infection" ***Nucleic Acids Res.*** 2009 Sep;37(17):5848-58. doi: 10.1093/nar/gkp604. Epub 2009 Aug 3.

Massalini S, Pellegatta S, Pisati F, Finocchiaro G, **Farace MG**, Ciafrè SA," Reelin affects chain-migration and differentiation of neural precursor cells" ***Mol Cell Neurosci****.* 2009 vol. 4, p. 341-349, ISSN: 1044-7431.

Evangelisti C, Florian MC, Massimi I, Dominici C, Giannini G, Galardi S, Buè MC, Massalini S, McDowell HP, Messi E, Gulino A**, Farace MG**, Ciafrè SA. MiR-128 upregulation inhibits Reelin and DCX expression and reduces neuroblastoma cell motility and invasiveness. ***The FASEB J.,*** 23(12):4276-87, 2009.

Mercatelli N, Coppola V, Bonci D, Miele F, Costantini A, Guadagnoli M, Bonanno E, Muto G, Frajese GV, De Maria R, Spagnoli LG, **Farace MG**, Ciafrè SA "The inhibition of the highly expressed miR-221 and miR-222 impairs the growth of prostate carcinoma xenograts in mice", ***PloS One***. 2008;3(12):e4029. doi: 10.1371/journal.pone.0004029. Epub 2008 Dec 24.

Galardi S., Mercatelli N., Giorda E., Massalini S., Frajese GV, Ciafrè SA, **Farace MG. "**MiR-221 and miR-222 expression affects the proliferation potential of human prostate carcinoma cell lines by targeting $p27^{Kip1}$", ***Journal of Biological Chemistry*****,** 282(32):23716-24, 2007**.**

le Sage C, Nagel R, Egan DA, Schrier M, Mesman E, Mangiola A, Anile C, Maira G, Mercatelli N, Ciafrè SA**, Farace MG**, Agami R. "Regulation of the p27(Kip1) tumor suppressor by miR-221 and miR-222 promotes cancer cell proliferation", ***EMBO J***., 26(15):3699-3708, 2007.

Ciafrè SA. Niola F, Giorda E, **Farace MG**, Caporossi D. **"**$CoCl_2$-simulated hypoxia in skeletal muscle cell lines: role of free radicals in gene up-regulation and induction of apoptosis", **Free Radic Res**, 41(4):391-401, 2007.

Rinaldi M., Signori E., Rosati P., Cannelli G., Parrella P., Iannace E., Monego G., Ciafrè SA., **Farace MG.,** Iurescia S., Fioretti D., Rasi G., and Fazio VM. "Feasibility of *in utero* DNA vaccination following naked gene transfer into pig fetal muscle: transgene expression, immunity and safety", ***Vaccine,***24,(21):4586-91, 2006.

Niola F., Evangelisti E., Campagnolo L., Massalini S., Buè MC., Mangiola A., Masotti A., Maira G., **Farace MG**., Ciafrè SA. "A plasmid-encoded VEGF siRNA reduces glioblastoma angiogenesis and its combination with interleukin-4 blocks tumor growth in a xenograft mouse model", ***Cancer Biology and Therapy***, 5(2), 2006

Ciafrè SA*, Galardi S*, Mangiola A, Ferracin M, Liu C-G, Sabatino G, Negrini M, Maira G, Croce CM, **Farace MG**. "Extensive modulation of a set of microRNAs in primary glioblastoma", ***Biochem. Biophys. Res. Comm.***, 334(4): 1351-8, 2005. *co-authors

Wannenes F, Ciafré SA., Niola F, Frajese G and **Farace MG.** "Vector-based RNA interference against Vascular Endothelial Growth Factor-A significantly limits vascularization and growth of prostate cancer *in vivo*", ***Cancer Gene Ther.***, 12(12):926-934, 2005.