

# MICHELA MUSCOLINI

## CONTACT DETAILS

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## ACTUAL POSITION

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### **April 2016 – to present Research Associate**

Istituto Pasteur Italia – Fondazione Cenci Bolognetti, Rome

- Genome-wide CRISPR-Cas9 loss-of-function screening to identify host restriction factors modulating oncolytic virotherapy
- Engineering of recombinant oncolytic viruses to improve oncolytic virotherapy for virus-resistant tumor models
- Oncolytic virotherapy: study of combination therapies in the treatment of virus-resistant cancer models
- Role of SIRT1 as a viral restriction factor in the sensitivity of prostate cancer cells to VSV mediated oncolysis

**Sector:** Cancer immunotherapy – Oncolytic virotherapy – Innate and adaptive immunity to viral pathogens – Cloning of new recombinant oncolytic viruses; Genome-wide CRISPR-Cas9 screening; Generation of CRISPR-Cas9 Knock-out clones

## PROFESSIONAL EXPERIENCE

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### **June 2015 – March 2016 Postdoctoral Researcher**

Dept. of Research, Advanced Diagnostics and Technological Innovations - Regina Elena National Cancer Institute, Rome

- Study of the metabolic plasticity of breast cancer stem cells and metastases.
- Analysis of breast cancer stem cells susceptibility to oncogenic PI3K-dependent signaling inhibitors identified through computational drug repositioning of FDA-approved compounds.

**Sector:** Cancer Metabolism – Signal transduction  
Extracellular Flux analysis (Seahorse XFp Analyzer)

### **August 2014 – March 2015 Postdoctoral Researcher**

Dept. of Biology and Biotechnology "Charles Darwin" Sapienza University of Rome

- Identification of PIP5K $\alpha$ /Vav1 complex as key mediator of early events of CD28-mediated cytoskeletal reorganization in T lymphocytes.

**Sector:** Molecular Immunology – Signal transduction  
Real Time PCR; signaling of lipids and Small GTPase (*in vitro* kinase assay; Small GTPase activation assay); protein-protein interaction (Co-IP); confocal microscopy (colocalization and protein recruitment studies)

### **January 2014 – July 2014 Postdoctoral Researcher**

Laboratory of Adaptive Immunology (Head of the Lab: Prof. Antonella Viola) Istituto Clinico Humanitas, Milano

- Collaboration to the research activity of Prof Antonella Viola and Dr Marinos Kallikourdis: study of the role of PIP5K $\beta$  in the early events of immunological synapse formation in T lymphocytes.

**Sector:** Molecular Immunology – Signal transduction  
Silencing and Real Time PCR; Calcium signaling

### **April 2011 – December 2013 Postdoctoral Fellow**

Laboratory of Molecular Immunology, Dept. of Biology and Biotechnology "Charles Darwin" (Head of the Lab: Prof. Loretta Tuosto) - Sapienza University of Rome

- Analysis of the molecular mechanisms regulating membrane phospholipid turnover in T lymphocytes: signaling pathways regulated by PI3K and PIP5Ks.
- Characterization of the signal transduction mechanisms regulating T lymphocyte proliferation and survival in both physiological and pathological conditions.

- Characterization of the molecular bases of inflammation in Multiple Sclerosis: targeting CD28/PI3K pathway as immunotherapeutic approach to dampen the inflammatory response.

**Sector:** Molecular Immunology – Signal transduction – Cellular Biology

Enzymatic activity assays (*in vitro* kinase assay; PI(4,5)P<sub>2</sub> Mass ELISA assay); confocal microscopy (protein recruitment and subcellular localization studies); measurement of intracellular calcium; transient gene silencing

### **November 2007 – February 2011 Ph.D. student**

Department of Cellular and Developmental Biology - Sapienza University of Rome.

- Characterization of the activity and post-transcriptional modification of mutants of p53 tumor suppressor
- Characterization of the signaling events regulating NF-κB activation and target gene expression in T lymphocyte

**Sector:** Cancer cells signalling – Molecular Immunology – Signal transduction

Flow cytometry analysis (Apoptosis, cell cycle and mitochondrial membrane depolarization analysis); *in vivo* ubiquitination assays; Site-specific mutagenesis

### **September 2008 – November 2008 Visiting PhD student**

Balbino Alarcón Laboratory – Dept. of Cellular Biology and Immunology Centro de Biología Molecular Severo Ochoa (Madrid, Spain)

- Acquisition of expertise in the use of confocal microscopy

**Sector:** Confocal microscopy – Signal transduction

## EDUCATION AND TRAINING

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**November 2011 Professional qualification (Biologist)** Sapienza University of Rome

### **February 2011 Ph.D. in Cellular and Developmental Biology**

Sapienza University of Rome (Advisor, Prof Loretta Tuosto)

Dissertation title: “*Characterization of a new cancer-associated mutant of p53 with a missense mutation (K351N) in the tetramerization domain.*”

### **March 2007 Biological Sciences Degree *cum laude***

Sapienza University of Rome (Advisor, Prof Loretta Tuosto)

Thesis title: “*Analysis of the molecular mechanisms regulating the apoptosis resistance of ovarian carcinoma cell lines in response to chemotherapy treatment.*”

### **March 2005 – March 2007 Internship for the Experimental Thesis in Biological Science**

Department of Cellular and Developmental Biology, Sapienza University of Rome

- Analysis of molecular pathways regulating apoptosis from p53 family proteins (p53 and p73) and the acquisition of chemotherapy resistance in cancer cell lines.
- Acquisition of techniques of cellular and molecular biology, and biochemistry.

## FELLOWSHIPS

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**January – December 2013 Research fellowship:** Fondazione Adriano Buzzati-Traverso

**Project:** Molecular and functional characterization of the complex PIP5K $\alpha$ /Vav-1 and its role in CD28-mediated activation of T cells.

**April 2011 – March 2012 Research fellowship:** Istituto Pasteur – Fondazione Cenci Bolognetti

**Project:** Role of type I phosphatidylinositol 4-phosphate 5-kinase alpha in the regulation of CD28-dependent signaling responses in T lymphocytes.

## TECHNICAL EXPERTISE

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### Cell biology

Eukaryotic cell cultures, T cell depletion of peripheral blood and primary cultures, breast cancer stem cells cultures, mammosphere formation assay, transfection of eukaryotic cells (lipofection; electroporation; nucleofection), RNA interference. Lentivirus production and transduction of human cells, Genome-wide CRISPR-Cas9 screening, generation of CRISPR-Cas9 Knock-out clones. 3D-sphereoid cultures.

Molecular biology	Cloning of plasmidic vectors, site-directed mutagenesis, plasmid DNA isolation, mini and maxi prep, restriction analysis; RNA extraction, reverse transcription, PCR, Real-Time PCR, Chromatin ImmunoPrecipitation (ChIP), luciferase assays, microRNA analysis. Cloning and rescue of recombinant oncolytic viruses.
Biochemistry	Native and denaturing protein extraction, cytosolic, nuclear and mitochondrial protein extraction, protein immunoprecipitation, SDS-PAGE, Western blot, <i>in vitro</i> kinase assay, measurement of PIP2 levels, ELISA.
Flow cytometry	Immunofluorescence analysis, cell death and cell cycle analysis, calcium flux measurement, Bead-based immunoassays (BD CBA Flex Set).
Microscopy techniques	Protein localization study, fluorescence and confocal microscopy, image analysis softwares.
Metabolic studies	Extracellular Flux analysis by using Seahorse XFp Analyzer.

## PERSONAL SKILLS

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Mother tongue	Italian
Other languages	- English - French
Communication skills	Good relationship skills; attitude to effectively collaborate and work in a team
Organisational/managerial skills	Excellent ability in coordinating and supervising resources; individual management of work; capacity to plan and to assign priorities; time management skill.
Computer skills	- Use of image analysis software (Zeiss LSM Image Browser, Leica LCS, ImageJ) - Good knowledge of graphic design applications (Adobe Photoshop™, Adobe Illustrator™) - Proficient in Microsoft Office™ tools
Driving license	B

## PUBLICATIONS

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- Palermo E, Alexandridi M, Di Carlo D, **Muscolini M**, Hiscott J. Virus-like particle - mediated delivery of the RIG-I agonist M8 induces a type I interferon response and protects cells against viral infection. *Front Cell Infect Microbiol.* 2022 Dec 14;12:1079926. doi: 10.3389/fcimb.2022.1079926.
- Muscolini M**, Hiscott, J, Tassone, E (2023). A Genome-Wide CRISPR-Cas9 Loss-of-Function Screening to Identify Host Restriction Factors Modulating Oncolytic Virotherapy. In: HDAC/HAT Function Assessment and Inhibitor Development. *Methods in Molecular Biology*, vol 2589: 379-399. Humana, New York, NY. [https://doi.org/10.1007/978-1-0716-2788-4\\_25](https://doi.org/10.1007/978-1-0716-2788-4_25).
- Ferrari M, Zevini A, Palermo E, **Muscolini M**, Alexandridi M, Etna M, Coccia E, Fernandez-Sesma A, Coyne C, Zhang D, Marques Júnior E, Olagnier D, Hiscott J. Dengue virus targets Nrf2 for NS2B3-mediated degradation leading to enhanced oxidative stress and viral replication. *J Virol* 2020 (24):e01551-20. doi: 10.1128/JVI.01551-20.
- Tassone E, **Muscolini M**, van Montfoort N, Hiscott J. Oncolytic virotherapy for pancreatic ductal adenocarcinoma: A glimmer of hope after years of disappointment? *Cytokine Growth Factor Rev.* 2020 Aug 8;S1359-6101(20)30191-X. doi: 10.1016/j.cytogfr.2020.07.015.
- Muscolini M\***, Tassone E, Hiscott J. Oncolytic Immunotherapy: Can't Start a Fire Without a Spark. *Cytokine Growth Factor Rev.* 2020 Aug 4;S1359-6101(20)30190-8. doi: 10.1016/j.cytogfr.2020.07.014. \*Corresponding author
- Dattilo R, Mottini C, Camera E, Lamolinara A, Auslander N, Doglioni G, **Muscolini M**, Tang W, Planque M, Ercolani C, Buglioni S, Manni I, Trisciuglio D, Boe A, Grande S, Luciani AM, Iezzi M, Ciliberto G, Ambs S, De Maria R, Fendt SM, Ruppin E, Cardone L. Pyrvinium Pamoate Induces Death of Triple-Negative Breast Cancer Stem-Like Cells and Reduces Metastases through Effects on Lipid Anabolism. *Cancer Res.* 2020 Jul 23. doi: 10.1158/0008-5472.CAN-19-1184.

7. Hiscott J, Alexandridi M, **Muscolini M**, Tassone E, Palermo E, Soultsioti M, Zevini A. The global impact of the coronavirus pandemic. *Cytokine Growth Factor Rev.* 2020 Jun;53:1-9. doi: 10.1016/j.cytogfr.2020.05.010. Epub 2020 May 28.
8. Palermo E, Acchioni C, Di Carlo D, Zevini A, **Muscolini M**, Ferrari M, Castiello L, Virtuoso S, Borsetti A, Antonelli G, Turriziani O, Sgarbanti M, and J Hiscott. Activation of latent HIV-1 T cell reservoirs with a combination of innate immune and epigenetic regulators. *J Virol* (2019) Aug 14. doi: 10.1128/JVI.01194-19.
9. Castiello L, Zevini A, Vulpis E, **Muscolini M**, Ferrari M, Palermo E, Peruzzi G, Krapp C, Jakobsen M, Olganier D, Zingoni A, Santoni A, and J Hiscott. An optimized retinoic acid-inducible gene I agonist M8 induces immunogenic cell death markers in human cancer cells and dendritic cell activation. *Cancer Immunol Immunother* (2019). Sep;68(9):1479-1492. doi: 10.1007/s00262-019-02380-2.
10. **Muscolini M\***, Castiello L, Palermo E, Zevini A, Ferrari M, Olganier D, and J Hiscott. SIRT1 modulates the sensitivity of prostate cancer cells to VSV oncolysis. *J Virol* (2019) 93: e00626-19. doi: 10.1128/JVI.00626-19.   
\*Co-corresponding author
11. Porciello N, Grazioli P, Campese AF, Kunkl M, Caristi S, Mastrogiovanni M, **Muscolini M**, Spadaro F, Favre C, Nunès JA, Borroto A, Alarcon B, Screpanti I and L Tuosto. A non-conserved amino acid variant regulates differential signalling between human and mouse CD28. *Nat Commun* (2018) 9:1080.
12. Di Nicola M, Apetoh L, Bellone M, Colombo MP, Dotti G, Ferrone S, **Muscolini M**, Hiscott J, Anichini A, Pupa SM, Braud F and M Del Vecchio. Innovative Therapy, Monoclonal Antibodies and Beyond. *Cytokine Growth Factor Rev.* 2017 38:1-9.
13. Olganier D\*, **Muscolini M\***, Coyne CB, Diamond MS and J Hiscott. Mechanisms of Zika Virus infection and neuropathogenesis. *DNA Cell Biol* (2016) 35:367-72. \*Equal contribution
14. Kallikourdis M, Trovato AE, Roselli G, **Muscolini M**, Porciello N, Tuosto L, and A Viola. Phosphatidylinositol 4-Phosphate 5-Kinase  $\beta$  controls recruitment of lipid rafts into the immunological synapse. *J Immunol* (2016) 196: 1953-1963.
15. Tuosto L, Capuano C, **Muscolini M**, Santoni A, and R Galandrini. The multifaceted role of PIP2 in leukocyte biology. *Cell Mol Life Sci* (2015) 72: 4461-74.
16. **Muscolini M**, Camperio C, Porciello N, Caristi S, Capuano C, Viola A, Galandrini R, and L Tuosto. Phosphatidylinositol 4-phosphate 5-kinase  $\alpha$  and Vav1 mutual cooperation in CD28-mediated actin remodeling and signaling functions. *J Immunol* (2015) 194: 1323-1333.
17. Camperio C\*, **Muscolini M\***, Volpe E, Di Mitri D, Mechelli R, Buscarinu MC, Ruggieri S, Piccolella E, Salvetti M, Gasperini C, Battistini L, and L Tuosto. CD28 ligation in the absence of TCR stimulation up-regulates IL-17A and pro-inflammatory cytokines in relapsing-remitting multiple sclerosis T lymphocytes. *Immunol Lett* (2014) 158: 134-142. \*Equal contribution
18. Palermo V, Mangiapelo E, Piloto C, Pieri L, **Muscolini M**, Tuosto L, and C Mazzoni. p53 death signal is mainly mediated by Nuc1(EndoG) in the yeast *Saccharomyces cerevisiae*. *FEMS Yeast Res* (2013) 13: 682-688.
19. **Muscolini M**, Camperio C, Capuano C, Caristi S, Piccolella E, Galandrini R, and L Tuosto. Phosphatidylinositol 4-Phosphate 5-Kinase  $\alpha$  activation critically contributes to CD28-dependent signaling responses. *J Immunol* (2013) 190: 5279-86.
20. **Muscolini M**, Montagni E, Palermo V, Di Agostino S, Gu W, Abdelmoula-Soussi S, Mazzoni C, Blandino G, and Tuosto L. The cancer-associated K351N mutation affects the ubiquitination and the translocation to mitochondria of p53 protein. *J Biol Chem* (2011) 286: 39693-702.
21. **Muscolini M**, Sajeva A, Caristi S and L Tuosto. A novel association between filamin A and NF- $\kappa$ B inducing kinase couples CD28 to inhibitor of NF- $\kappa$ B Kinase  $\alpha$  and NF- $\kappa$ B activation. *Immunol Lett* (2011) 136: 203-212.
22. **Muscolini M**, Montagni E, Caristi S, Nomura T, Kamada R, Di Agostino S, Corazzari M, Piacentini M, Blandino G, Costanzo A, Sakaguchi K, and L Tuosto. Characterization of a new cancer-associated mutant of p53 with a missense mutation (K351N) in the tetramerization domain. *Cell Cycle* (2009) 8: 1-10.
23. **Muscolini M**, Cianfrocca R, Sajeva A, Mozzetti S, Ferrandina G, Costanzo A and L Tuosto. Trichostatin A up-regulates p73 and induces Bax-dependent apoptosis in cisplatin-resistant ovarian cancer cells. *Mol Cancer Ther* (2008) 7: 1410-1419.
24. Annibaldi A, Sajeva A, **Muscolini M**, Ciccocanti F, Corazzari M, Piacentini M and L Tuosto. CD28 ligation in the absence of TCR promotes RelA/NF- $\kappa$ B recruitment and trans-activation of the HIV-1 LTR. *Eur J Immunol* (2008) 38: 1446-1451.
25. Cianfrocca R, **Muscolini M**, Marzano V, Annibaldi A, Marinari B, Levrero M, Costanzo A and L Tuosto. RelA/NF- $\kappa$ B recruitment on the *bax* gene promoter antagonizes p73-dependent apoptosis in costimulated T cells. *Cell Death Differ* (2008) 15: 354-363.