BIOGRAPHICAL SKETCH
NAME: RAFFAELLA DI MICCO

POSITION TITLE: GROUP LEADER AT THE TELETHON INSTITUTE FOR GENE THERAPY, SAN RAFFAELE HOSPITAL

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
University of Naples "Federico II"	M.Sc	July 2003	Cancer Metastasis
European School of Molecular Medicine (SEMM)	PhD	2004-2008	DNA damage checkpoint activation during oncogene-induced senescence
IFOM Foundation, Milan, Italy (Fabrizio d'Adda di Fagagna's lab)	Postdoc	2008-2010	Interplay between chromatin and DNA damage signaling in senescence and cancer
New York University, New York, USA (Eva Hernando's lab)	Postdoc	2010-2015	Epigenetics and Transcription in stem cells and cancer

A. Personal Statement

The molecular mechanisms of stress responses in stem cells and during cancer progression have always been my main area of interest and fascination. Over the past 15 years I have worked on several different aspects of this incredibly broad field. During my PhD training I investigated the molecular mechanisms by which activated oncogenes induce DNA damage and cellular senescence. I was able to demonstrate that uncontrolled hyper-proliferation of oncogene expressing cells ultimately leads to DNA breaks and the activation of senescence as a tumor suppressor mechanism (*Di Micco et al. Nature 2006*). After graduation, I focused on the study of alterations of chromatin structure during senescence and discovered that heterochromatin formation induced by oncogenes is the consequence of DNA replication stress in the cells. I studied how alterations in chromatin could lead to new targeted therapies aimed to re-establish normal epigenetic patterns in cancer settings *(Di Micco et al., Nat Cell Biol 2011; Sulli et al., Nature Rev Cancer 2012*). In 2010, I moved to United States for a postdoctoral training in the laboratory of Dr. Eva Hernando at NYU School of Medicine to perform research aimed at understanding the epigenetic and transcriptional regulation in stem cell and during cancer development. In the first year of my postdoctoral training I was awarded with a prestigious European Molecular Biology Organization (EMBO) fellowship and in the second year I received a postdoctoral fellowship from Human Frontier Science Project (HFSP). Soon after I joined the lab, I became part of a study focused on the role of miRNA regulation in melanoma metastasis that deserved me a co-authorship in a manuscript published in *Cancer Cell*. Later, by using genetic and chemical-based approaches, both targeted and genome-wide, I identified novel molecular mechanisms involved in stem cell maintenance, with a particular focus on the epigenetic and transcriptional regulator BRD4. These findings were published in *Cell Reports* and as leader of the project I am the corresponding author (Di Micco et al., 2014). This work was supported by the New York Stem Cell Foundation (NYSCF) Druckenmiller postdoctoral fellowship. The fellowship program gave me the opportunity to

gain visibility and to establish collaborations and interactions with outstanding scientists in the field of stem cell biology field. More recently, I contributed to a comprehensive study on the mechanisms of BRD4-dependent regulation of enhancer elements in melanoma survival (*Fontanals-Cirera Mol Cell 2017*) that led to the identification of new therapeutic targets for cancer treatment. The postdoctoral experience in US made me a stronger and motivated scientist and contributed to prepare myself for a career as an independent investigator. Seeking for a group leader position, I took part to selective and competitive job interview processes in leading institutions in Europe and United States. I decided to establish my research team at the San Raffaele-Telethon Institute for Gene Therapy (SR-TIGET) within the San Raffaele Hospital, in Milan in early 2016. The research in my lab capitalizes on the scientific expertise of my PhD and postdoctoral trainings in DNA damage, senescence, epigenetics and cancer and involves, as a model system, the human hematopoietic stem and progenitor cells (HSPCs). The main goal of my lab is to dissect the interplay between chromatin and DNA damage upon stress in normal stem cells and in the context of malignant hematopoiesis with the final aim to develop hypothesis-driven strategies for therapeutic applications. I envision a research career that is pioneering and translational. Our laboratory perfectly integrates within a multidisciplinary team of basic biologists, statisticians, hematologists, clinicians with different yet complementary sets of expertise and takes advantage of relevant human patient samples. Our institute is an internationally recognized research center in the field of normal and malignant hematopoiesis and provided me a fully equipped and renovated lab space, state-of-art technologies and cutting-edge support facilities and infrastructures to promote scientific excellence and innovation.

B. Positions and Honors

Positions and Employment

2004-2008 Predoctoral Student at the European School of Molecular Medicine (SEMM), IFOM, Milan
2008-2010 Postdoctoral researcher at IFOM, Milan
2010-2015 Postdoctoral researcher at the NYU Langone Medical Center
2015- present Group Leader at the San Raffaele Telethon Institute for Gene Therapy within the San Raffaele Hospital

Professional Memberships

2010 Member of American Association Cancer Research, AACR
2010 Member of International Society for stem cell research, ISSCR
2013 Member of New York Stem Cell Foundation, NYSCF
2016 Member of European Society of Cell and Gene Therapy (ESCGT)
2016 Member of the European Hematology Association (EHA)
2017 Member of Società Italiana di Biofisica e Biologia Molecolare (SIBBM)
2019 Member of the American Society of Hematology (ASH)

Reviewer Experience

2015-present Journal Reviewer: *Cell, Nature Cell Biology, Nature Communications, Molecular Cell, Cell Reports, Aging Cell, Cell Death and Disease, Faseb J, Trends in Cell Biology, Plos One, Developmental Cell, Cells, Frontiers in Oncology, Mechanisms of Ageing and Development*
2015-present Grant Reviewer: *Italian Ministry of Health, Polish National Science Centre, French National Research Agency (ANR), Swiss National Science Foundation, Atip - Avenir program by INSERM*
2019-present Abstract Reviewer: *Annual Meeting of the International Society of Stem Cell Research (ISSCR Boston 2020); Annual Meeting of the European Hematology Association (EHA Frankfurt 2020); International Cell Senescence Association (Athens 2019).*
2019 Guest Editor of the special issue: “Advances in Senescence” in *Mechanisms of Ageing and Development*

Honors

2007 Research award P. SCHLECTER e L. CESCATTI, Foundation for Cancer Research
2010 European Molecular Biology Organization (EMBO) postdoctoral fellowship: 'Impact of melanocyte differentiation during melanoma pathogenesis'
2011 Human Frontier Science Project (HFSP) postdoctoral fellowship: 'Epigenetic regulation of melanocyte differentiation during melanoma pathogenesis'
2013 New York Stem Cell Foundation Druckenmiller fellowship: 'Role of BRD proteins in stem cell regulation and cancer"
2014 Offered a Group Leader position at Research Center for Molecular Medicine of the Austrian academy of Science, CEMM, Vienna. Declined
2014 Offered a Group Leader position at Istituto Nazionale di Genetica Molecolare INGM. Declined
2015 Mobility Research Program of Human Frontier Science Project (HFSP)
2016 Awarded a Telethon Grant
2016 Awarded 'Pilot and Seed Grant' from San Raffaele Hospital.
2019 Selected for participation to the Interstellar Initiative of the New York Academy of Science and Japan Agency for Medical Research and Development
2019 Passed a pre-selection stage for the EMBO Young Investigator Program
2019 Awarded "Under 40 in Hematology Award" for Best study in Translational Medicine form the Italian Society of Hematology
2020 ASH Global Research Award
2020 New York Stem Cell Foundation Robertson Investigator

Other Activities

2019-present	Board Member of the "Cell and Gene Therapy" International PhD program in Molecular Medicine at University Vita-Salute San Raffaele.
2016-present	Lecturer for "Gene and Cell Therapy" course at the Faculty of Medical Biotechnologies at University Vita Salute San Raffaele.
2016-present	Academic Supervisor of 6 Master students, 1 Medical Doctor student, 4 PhD students, 6 postdoctoral fellows.
2017-present	Member of INCIPIT (Innovative Life Science PhD program in South Italy) Scientific Evaluation Committees (SECs). COFUND scheme, European Commission.
2017-present	Graduate Student Advisor/Examiner, University Vita-Salute San Raffaele, Milan, Italy
2019	SR-TIGET scientific retreat, 200 participants, Milan, Italy (Scientific organizer) "Mentoring Moments" initiative to support career development of young scientists at San Raffaele Hospital, Milan, Italy

C. Contributions to Science

Early publications during my PhD training directly addressed the impact of activated oncogenes on cellular senescence and on dynamics of DNA replication in normal cells. At that time, oncogene-induced senescence was thought to be a program of mere proliferative arrest. I demonstrated that the

uncontrolled hyper-proliferation of oncogene expressing cells ultimately leads to DNA breaks and the activation of tumor suppressor mechanisms. When tumor suppressors and cell cycle inhibitors are inactivated, oncogene-expressing cells can bypass cellular senescence and proliferate bearing DNA breaks and being genomic unstable. This study represents a cornerstone in the senescence and cancer field. This study deserved publication in the prestigious journal *Nature* and has been heavily cited underlining the relevance of my findings. In addition, I demonstrated that the activation of DNA damage-response (DDR) is conserved in murine settings. I also authored a comprehensive review on mechanisms of oncogene-induced senescence in Trends in Cell Biology.

a) **Di Micco R.,** Fumagalli M., Cicalese A., Piccinin S. Gasparini P., Luise C., Schurra C.,Garre' M., Nuciforo P. Bensimon A., Maestro R., Pelicci P.G., and d'Adda di Fagagna F. Oncogene-induced senescence is a DNA-damage checkpoint response triggered by DNA hyper-replication. **Nature**, 2006.
   News and views by L. Cao and T. Finkel in Nature Medicine.
   Faculty of 1000: Highlighted as "Must read". FFa = 9
b) **Di Micco R.,** Cicalese A., Fumagalli M., Dobreva M., Verrecchia A., Pelicci P.G., and d'Adda di Fagagna F. DNA damage response activation in mouse embryonic fibroblasts undergoing replicative senescence and following spontaneous immortalization. **Cell Cycle**, 2008.
c) **Di Micco R.,** Fumagalli M. and d'Adda di Fagagna F. Breaking news: high speed run away ends in arrest. How oncogenes induce senescence. **Trends in Cell Biology**, 2007.

During the second part of my PhD training and in the following years after graduation, I focused on the study of alterations of chromatin structure during senescence and discovered that heterochromatin formation induced by oncogenes is the consequence of DNA replication stress in the cells. In particular, I found that heterochromatin induced upon genotoxic stress restrains the activation of DDR. Targeted therapy that aims to perturb heterochromatin in oncogene-expressing cells leads to DDR activation and spreading, resulting in cell death. These findings suggest that novel targeted therapies aimed to re-establish epigenetic patterns in tumor cells could be therapeutically exploited in cancer settings. This study deserved a publication in *Nature Cell Biology*. We have also published a comprehensive review in *Nature Reviews Cancer* that analyzed the state of art of the potential interplay between heterochromatin and DDR in senescence and cancer. During that time, I was also involved in other studies elucidating the role of DNA replication stress at telomeres and the impact of reactive oxygen species in mediating oncogene-induced senescence.

a) **Di Micco R.,** Sulli G., Dobreva M., Liontos M., Botrugno OA., Gargiulo G., dal Zuffo R., Matti V., d'Ario G., Montani E., Mercurio C., Hahn W.C., Gorgoulis V.G., Minucci S. and d'Adda di Fagagna F. Interplay between oncogene-induced DNA damage response and heterochromatin in senescence and cancer. **Nature Cell Biology**, 2011.
   Commentary by P. Adams in Nature Cell Biology.
   Commentary by T. Halazonetis in Cell Cycle.
   Faculty of 1000: Highlighted as "Must read". FFa = 12
b) Suram A, Kaplunov J, Patel PL, Ruan H, Cerutti A, Boccardi V, Fumagalli M, **Di Micco R,** Mirani N, Gurung RL, Hande MP, d'Adda di Fagagna F, Herbig U. Oncogene-induced telomere dysfunction enforces cellular senescence in human cancer precursor lesions. **EMBO J.,** 2012.
   Commentary by K.L. Rudolph in the same issue of EMBO Journal
   Commentary by J.J. Jacobs in Nature Reviews Molecular and Cellular Biology
c) Sulli G., **Di Micco R.** and d'Adda di Fagagna F. Crasstalk between chromatin state and DNA damage response in senescence and cancer. **Nat Rev Cancer.** Oct 2012.

d) Ogrunc M., **Di Micco R.**, Liontos M., Bombardelli L., Mione M., Fumagalli M., Gorgoulis V.G and d'Adda di Fagagna F. Oncogene-induced reactive oxygen species fuel hyper-proliferation and DNA damage response activation. **Cell Death and Differentiation**, 2014

In 2010, I moved to US for a postdoctoral training in the laboratory of Dr. Eva Hernando at NYU School of Medicine. The Hernando's lab focuses on understanding the role of epigenetic regulators (miRNA and chromatin remodelers) in melanoma initiation and progression. Soon after I joined the lab I became part of a study focused on the role of miRNA in melanoma (miR30b/30d) are over-expessed in melanoma and directly regulate the expression of GalNac transferases, to enhance invasion and immunosuppression during melanoma metastasis. As part of this study I deserved a co-authorship in a manuscript published *Cancer Cell.* My main scientific interest remained understanding the epigenetic and transcriptional regulation of stem cell identity and cancer development. I first focused on the role of epigenetic readers, bromodomain and extra-terminal domain proteins (BET) in controlling stem cell identity and cell fate decisions. I discovered that BRD4, a BET family member is a critical regulator of stemness. BRD4 chemical and genetic inhibition impairs self-renewal capacity of human embryonic stem cells. Furthermore, BRD4 depletion drives cell differentiation toward the neuroectodermal lineage *in vitro* and in teratoma assays *in vivo*. Combining cell and molecular biology approaches, together with next generation sequencing methods, I discovered a novel mechanism by which BRD4 controls the transcriptional elongation of key cell identity genes that are associated with so-called super-enhancers (SE) and regulate lineage specification. These findings are published in *Cell Reports* and as leader of the project I am co-corresponding author. I pioneered the field of epigenetics in a lab with no previous experience and I opened new research lines focused on transcriptional and epigenetic regulation of melanoma genesis and metastasis. In particular, by using an integrative epigenomic approach I demonstrated that BRD4 regulates the expression of important melanoma oncogenes by binding to their enhancer regulatory elements. Conversely, ChIP-seq analysis for histone repressive marks and chromatin repression indicated repressive domains spanning kilobases at tumor suppressors genes. This innovative approach led to the identification of AMIGO2 as a novel oncogene and therapeutic target in melanoma.

a) Gaziel-Sovran A, Segura MF, **Di Micco R**, Collins MK, Hanniford D, Vega-Saenz de Miera E,Rakus JF, Dankert JF, Shang S, Kerbel RS, Bhardwaj N, Shao Y, Darvishian F, Zavadil J, Erlebacher A, Mahal LK, Osman I, Hernando E. miR-30b/30d regulation of GalNAc transferases enhances invasion and immunosuppression during metastasis. **Cancer Cell,** 2011.
b) **Di Micco R.§,** Fontanals-Cirera B., Low V., Ntziachristos P., Yuen S., Lovell C., Dolgalev I., Yonekubo Y., Zhang G., Rusinova E., Gerona-Navarro G., Canamero M., Ohlmeyer M., Aifantis I., Zhou M.M., Tsirigos A.§ and Hernando E.§ Control of embryonic stem cell identity by BRD4-dependent transcriptional elongation of super-enhancer associated pluripotency genes. **Cell Reports**, 2014. §Corresponding author.
c) Fontanals-Cirera B., Hasson, D, Vardabasso, C., **Di Micco R,** Agrawal P, Chowdhury A Gantz, de Pablos-Aragoneses A, Morgenstern A, Wu, P.,Filipescu,D., Valle-Garcia D., Darvishian F, Roe JS, Davies MA, Vacok CR, Hernando E, Bernstein E. Harnessing BET inhibitor sensitivity reveals AMIGO2 as a melanoma survival gene. **Mol Cell** 2017.

In early 2016 I established my own laboratory at the San Raffaele Hospital. The research lines of my lab fully capitalize on my expertise in the field of DNA damage and epigenetics. Given the longstanding leadership of the host institution in the field of genetic engineering of human hematopoiesis and in innovative translational research applied to hematological malignancies, we chose hematopoietic cells as an experimental model system. In particular, research in my lab focuses

on understanding the cellular responses to stress in hematopoietic stem cells and in hematological malignancies. Research projects in my lab aim at dissecting the contribution of senescence in the aged hematopoietic niche and at modeling the role of senescence programs in response to therapy and relapse.

a) Schiroli,G. Conti A., Ferrari S., della Volpe L., Jacob A., Albano L., Beretta S., Calabria A., Vavassori V., Gasparini P., Salataj E., Ndiaye-Lobry, Chaumeil, J., Montini, E., Ivan Merelli, Genovese P. §, Naldini L. §and **Di Micco R. §**. Precise Gene Editing Preserves Hematopoietic Stem Cell Function Following Transient p53-Mediated DNA Damage Response. *Cell Stem Cell 2019.* & last and corresponding author.

b) Conti A. and **Di Micco R.§.** p53 activation: a checkpoint for precision genome editing? *Genome Medicine, 2018.*

c) **Di Micco R.** and Montini E. §. De(bar)coding aged hematopoiesis. *Blood 2018*

d) **Di Micco R. *§.*** Sensing the breaks: cytosolic chromatin in senescence and cancer. *Trends in Molecular Medicine, 2017.*

e) Gnani D., Crippa S., della Volpe L., Rossella V., Conti A., Lettera E., Rivis S., Ometti M., Fraschini G., Bernardo and **Di Micco R.§.** A pre-senescence program in aged mesenchymal stromal cells contributes to the activation of inflammatory genes in hematopoietic stem and progenitor cells. *Aging Cell 2019.*

f) Gambacorta V. Gnani D., Vago L. and **Di Micco R§**. *Review in Frontiers in Cell and Developmental Biology.* Topic: Chromatin Traits in Human Diseases

g) **Di Micco R. §**, Krizhanovsky V. Baker D. and d'Adda di Fagagna§. Cellular Senescence: from mechanisms to therapy. *Nature Reviews Molecular and Cellular Biology 2021* **(**Special Issue on Aging). § corresponding author

h) Biavasco R * Lettera E*, Cesana D, Conti A., **Di Micco R.§** and Montini E.§. Oncogene induced senescence in hematopoietic progenitors features myeloid-restricted hematopoiesis, chronic inflammation and histiocytosis. In press *Nature Communications*. § co-last and co-corresponding author

i) Gambacorta V., Gnani D., Santaniello F., **Di Micco R.§ and L. Vago§**. The epigenetic landscape of acute myeloid leukemia post-allo HSCT identifies PRC2 as a critical mediator of leukemia immune-escape. Submitted to *Cancer Discovery* § co-last and co-corresponding author

D. Past and Ongoing Research Support

2016-2019 OSR Pilot and Seed grant 2015: Identification and targeting of epigenetic drivers of immune evasion in AML relapses after allogeneic HSCT
2016-2021 Telethon Grant: Core funding
2019-2020 Leukemia Research Foundation
2019-2021 European Hematology Association Advanced Research Grant
2019-2022 Human Frontier Science Program Career Development Award
2019-2020 Interstellar Initiative on Healthy Longevity from New York Academy of Sciences and Japan Agency for Medical Research and Development
2020-2025 My First AIRC grant Italian Association for Cancer Research
2020-2021 Catalyst Award on Healthy longevity from Japan Agency for Medical Research and Development
2021-2022 ASH Global Research Award
2021-2026 New York Stem Cell Investigator Robertson Award
2021-2023 NC3Rs CRACK-IT Challenge
2022-2027 European Research Council Consolidator Grant 2020