
BIOGRAPHICAL SKETCH

NAME: Neri, Francesco

eRA COMMONS USER NAME (credential, e.g., agency login): F.NERI

POSITION TITLE: Full Professor of Molecular Biology

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 Siena, Italy	BS	09/2005	Molecular Biology
University of Siena, Italy	Master Degree	09/2007	Molecular Biology
University of Siena, Italy	PhD	12/2011	Biotechnology
Human Genetics Foundation, Torino	Postdoc	09/2015	Epigenetics

A. Personal Statement

I obtained my PhD in Biotechnology in Siena (Italy) working on embryonic stem cells epigenetics. Then I worked as postdoc between Human Genetics Foundation (HuGeF) in Torino (Italy) and the Radboud University Medical Centre, Nijmegen (Netherlands) where specialized my research on the DNA methylation specific epigenetic mark on stem cell, differentiation and colon cancer. During this period, I characterized new mechanisms of gene transcriptional regulation, developed new epigenomic genome-wide methods and identified the role of the intragenic methylation. In 2016, I was appointed as Group Leader of the “Epigenetics of Aging Research Group” at the Fritz Lipmann Leibniz Institute on Aging (FLI) in Jena (Germany). My research was supported by the Sofja Kovalevskaja starting grant of the von Humboldt foundation, and it was focused on the aging-dependent epigenetic aberrations occurring in adult stem cells promoting colon cancer. In 2021, I moved my laboratory at the University of Torino, where I was appointed as Associate Professor and later as Full Professor of Molecular Biology. In Torino, I am leading the research group of Epigenetics of Aging & Cancer at the Molecular Biotechnology Center (MBC) in Torino. My current research focuses on inflammaging, intestinal aging, epigenetic drifts and how aging functionally impacts on colon cancer initiation. In summary, I have the expertise, leadership, training, and motivation necessary to successfully carry out the proposed research project that would allow my research to deeper study the process of colon cancer initiation to finalize the work done on these 4 years.

Ongoing and recently completed projects that I would like to highlight include:

Sofja Kovalevskaja (ITA1164767SKP)

Neri (PI)

2016-2021

Aging induced epigenetic alterations of intestinal stem cells promoting tissue dysfunction and cancer

Fritz Thyssen Foundation (10.17.2.021MN)

Neri (PI)

2017-2019

Functional role of DNA methylation associated mutations in driving age-related clonal dominance and colorectal cancer in human

DFG grant, NE 2144/5-1

Neri (PI)

2021-2023

Characterization of dormant intestinal stem cells by a novel Optical Stem Cell Activity Reporter

AIRC (MFAG 2021 ID 26038)

Neri (PI)

2022-2026

Origin of the aging-associated intestinal epigenetic drift and its impact in cancer development

Fondazione Molinette 2023

Neri (PI)

2024-2025

Antioxidant Treatment for Aging-associated Gut Inflammation

Citations:

1. Omrani, O., Krepelova, A., ... **Neri, F.** (2023). IFN γ -Stat1 axis drives aging-associated loss of intestinal tissue homeostasis and regeneration. **Nature Communications**, 14, 6109.
2. Lu, J., Annunziata, F., ... and **Neri, F.** (2022). Establishment and evaluation of module-based immune-associated gene signature to predict overall survival in patients of colon adenocarcinoma. **Journal of Biomedical Science** 29, 81.
3. Rasa, S.M.M., Annunziata, F., ... **Neri, F.** (2022). Inflammaging is driven by upregulation of innate immune receptors and systemic interferon signaling and is ameliorated by dietary restriction. **Cell Reports** 39, 111017.
4. Freter, R., Falletta, P., ... and **Neri, F.** (2021). Establishment of a fluorescent reporter of RNA-polymerase II activity to identify dormant cells. **Nature Communications** 12, 3318–16.
5. Ermolaeva M. *, **Neri F. ***, Ori A. *, Rudolph K.L. * (2018). Cellular and epigenetic drivers of stem cell ageing. **Nature Reviews Molecular Cell Biology**, 20(Suppl. 1), 667. (* Corresponding authors).
6. **Neri, F.***, et al. (2017). Intragenic DNA methylation prevents spurious transcription initiation. **Nature**, 543(7643), 72–77. (* Corresponding authors).

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2024 – Present	Full Professor, University of Torino, Italy
2023 – Present	Member of the National PhD school Life Course Research
2022 – Present	Member of the PhD school Complex System for Quantitative Biomedicine
2022 – Present	Scientific Council of the Research Centre for Molecular Systems Biology, Torino
2021 – Present	Guest Scientist, Leibniz Institute on Aging – FLI, Jena, Germany
2021 – 2023	Associate Professor, University of Torino, Italy
2017 – 2020	Member of the Internal Council , Leibniz Institute on Aging – FLI, Jena, Germany
2016 – Present	Member of the PhD school Leibniz Graduate School on Aging
2016 – 2021	Group Leader, Leibniz Institute on Aging – FLI, Jena, Germany
2015 – 2016	EMBO fellow, Radboud University Medical Centre, Nijmegen, Netherlands

Honors

2014	Nicolo Copernico Award for the best year research article from an Italian researcher under 35 years
2015	Travel Grant SIBBM Award
2015	EMBO Short Term Fellowship Award
2016	Sofja Kovalevskaja Award
2017	GSCN 2017 Young Investigator Award
2023	Fondazione Molinette Award

C. Contributions to Science

1. Angiogenesis

During my master thesis I worked in the laboratory of Molecular Biology at University of Siena focused on the tumour-related angiogenesis biology and I contributed to the study of the role of VEGFR3 and FOSL1 in intracellular signalling and cell adhesion. In particular, we demonstrated that extracellular matrix induces an activation of the VEGFR3 independent from its kinase activity and that FOSL1 regulates endothelial cells assembly by repressing the transcription of integrins.

(Galvagni, Circulation Research 2010; Evellin, MCB 2013)

2. MYC regulates PRC2 transcription

During my PhD, I studied the role of the transcription factor MYC, a potent oncogene, often found overexpressed in several cancers. MYC regulates cell cycle and cell metabolism by directly activating the transcription of thousands of gene. It is involved also in stemness maintenance and in reprogramming of differentiated cells. I demonstrated that MYC positively regulates, both in stem and in differentiated cells, the expression of all components of the Polycomb repressive complex 2 (PRC2) to repress differentiation genes. This regulation is necessary for pluripotency preservation in stem cells and for promoting dedifferentiation program in adult differentiated cells. My work was the first claiming that overexpression of MYC, as well as increases cell proliferation, also regulates adult cells epigenetic identity promoting in this way dedifferentiation and malignancy of transformed cells.

(Neri, MCB 2012; Krepelova, Neri, PlosOne 2014)

3. DNA methylation of developmental gene promoters

During my postdoc experience I focused on the role of DNA methyltransferases in embryonic stem cells. I found that PRC2 recruits DNMT3L (passive way) and TET1 (active way) to maintain the developmental associated gene promoters in a hypomethylated state to permit their further activation during differentiation. PRC2-target genes are often found hypermethylated on their promoters in human cancers. My work explain how these regions are maintained hypomethylated in stem cells laying the foundation for the understanding of how they become hypermethylated in differentiated or transformed cells.

(Neri, Cell 2013; Neri, Genome Biology 2013)

4. TET1 in colon cancer

This work is the concrete proof of how my studies in stem cells are of great impact for the understanding of tumorigenesis. I demonstrated that TET1 is strongly downregulated in human colon cancers and its re-expression in colon cancer cells inhibits in vitro cell proliferation and in vivo tumour growth. TET1 repression occurs already in first stages, suggesting that it is an early event in tumorigenesis. TET1 knockdown or overexpression in not transformed cells (such as MEFs) promotes or inhibits cell proliferation, respectively. Thus, TET1 is a powerful oncosuppressor by acting on cell proliferation in differentiated cells. I showed that TET1 directly demethylates the promoter of the WNT pathway inhibitors (such as DKKs and SFRPs) activating their transcription. These genes are often found repressed, by DNA methylation, in colon cancers, because of the loss of TET1 during cell transformation.

(Neri, Oncogene 2014; Neri, NAR 2015)

5. DNA demethylation of active gene promoters

In this work I developed a new method for mapping along the genome the 5-formyl-cytosine and 5-carboxyl-cytosine, which are oxidative forms of methyl-cytosine and marks of active DNA demethylation sites. This method is a powerful tool for the study of DNA demethylation events that often take place in cancer development. Moreover, by using these approaches I explained in detail the actual promoter DNA methylation/demethylation

dynamics in stem cells favoring the understanding of how some oncosuppressor promoters can become hypermethylated in cancer development.

(Neri, Cell Reports 2015; Neri, Oncotarget 2015; Neri, Nature Protocols 2016)

6. Functional role of intragenic DNA methylation

DNA methylation is a heritable epigenetic modification required for embryonic development, and it causes transcriptional repression, when established on gene promoters. Recent studies reported that Dnmt3b binds preferentially to the gene bodies by interacting with the histone modification H3K36me3. The molecular and biological functions of intragenic DNA methylation is still unknown, although deregulation of this epigenetic feature has been associated with several diseases. Here I show that the Dnmt3b-dependent intragenic DNA methylation protects the gene body from RNA Polymerase II (RNA Pol II) spurious entry and cryptic transcription initiations. By using different genome-wide approaches, I demonstrate the functional role of the Dnmt3b-dependent intragenic DNA methylation, and the existence of a RNA Pol II-triggered epigenetic crosstalk involving SetD2, H3K36me3, Dnmt3b and DNA methylation to ensure gene transcription initiation fidelity.

(Neri, Nature 2017)

7. Transcriptional and epigenetic alterations during aging

In 2016, I have been awarded the Sofja Kovalevskaja Award starting grant for studying epigenetics of stem cells in intestine during aging and diseases at the Leibniz Institute on Aging, Fritz Lipmann Institute, Jena, Germany. My experience and expertise in epigenetics, embryonic stem cells and in colon cancer, joined together with that in adult stem cells and aging present at the FLI institute made possible the establishment of my research group. In the 2016-2021 period, we established protocols, animal models, NGS methods and specific bioinformatic pipelines, collaborations with scientists in this field and clinicians for studies on human samples. The goal of the projects at FLI was the identification and characterization of transcriptional and epigenetic alterations occurring in aging mouse and human intestinal stem cells.

(Lu, Scientific Reports 2021; Freter, Nature Communications 2021; Krepelova, Methods Molecular Biology 2021; Nunna, Molecular Cancer Therapy 2021; Sirvinskis, Science 2022; Rasa, Cell Reports 2022; Omrani, Krepelova, Nature Communications 2023).

8. Intestinal DNA methylation drift promoting colon cancer development

During life-time, adult stem cells accumulate epigenetic alterations that lead to the appearance and expansion of mutant stem cell clones. These cells lead to tissue dysfunction and cancer. Our group is interested to understand the molecular mechanisms driving the fixation of these mutant clones and tumorigenesis. By employing cutting-edge technologies including single-cell genome-wide experiments, we analyzed primary cells and tissues to mechanistically dissect the origin and to understand the function of these epigenetic alterations, mainly focusing on DNA methylation.

(Krepeleva, Nature Aging, under revision)

Complete List of Published Work in MyBibliography:

https://www.ncbi.nlm.nih.gov/myncbi/1VeB7_BFbv1AU/bibliography/public/