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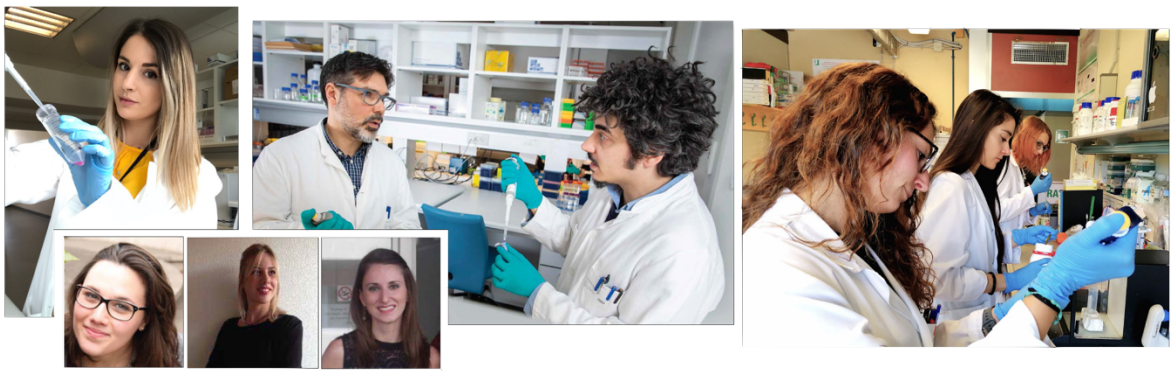
Photo of the Group (former and previous members):



Interest in NO and Cancer:

Cancer is characterized by heterogeneous molecular mechanisms and signaling pathways, which are induced by adaptive responses to stressful conditions and lead to the selection of cells characterized by therapy resistance, capability to migrate and invade distant tissues. In this context, my team has focused on *S*-nitrosylation (SNO) – the reversible modification of cysteine residues by nitric oxide (NO) – and discovered that conditions of deregulated SNO, e.g., those resulting from deficiency in the denitrosylase *S*-nitrosoglutathione reductase (GSNOR), are associated with cancer and human disease.
Our main focuses are to understand how SNO:

1. modifies protein structure-function and affects cancer growth and metabolism;
2. cross talks with other signaling networks (e.g., phosphorylation or ubiquitination);
3. contributes to processes sustaining malignancy.

In these subject areas, our research group aims at understanding the role of GSNOR and SNO in controlling mitochondrial homeostasis. In particular, we are exploring how SNO regulates the activity of proteins involved in mitochondrial dynamics and mitophagy, and if any dysregulation (such as when GSNOR is mutated or lost) can act as common molecular mechanism of cancer and aging, which is, indeed, a major risk factor for cancer development. A topic we are intensely focusing on is to unveil the functional role of SNO in the development of aggressive and invasive phenotype of cancer cells, with particular emphasis in its ability to modify specific proteins mediating cell death resistance, epithelial-to-mesenchymal transition, metabolism rewiring and autophagy.
By means of state-of-the-art technology and collaborations with internationally renowned laboratories actively engaged in cancer research and redox biology, we also seek to understand if, and how, SNO tunes cellular antioxidant response and, as a consequence, all the processes whose correct activation depend on the controlled production of reactive oxygen species (ROS) as second messengers, such as T cell activation and immune competence.

Selected publication:

1. Di Leo L., Bodemeyer V., Bosisio F.M., Claps G., Carretta M., Rizza S., Bordi M., Pires Pacheco M., Di Martino J., Bravo-Cordero J.J., Madsen D.H., Guldberg P., **Filomeni G.**, Sauter T., Robert C., De Zio D., Cecconi F. (Accepted) Loss of Ambra1 promotes melanoma growth and invasion. ***Nat. Commun.***

2. Maiani E., Milletti G., Nazio F., Grønbæk Holdgaard S., Bartkova J., Rizza S., Cesatini V., Lorente M., Di Marco M., Cianfanelli V., D'Acunzio P., Di Leo L., Rasmussen R., Montagna C., Gabicagogeascoa E., Salvador N., Pupo E., Carinci M., De Stefanis C., Gallo A., **Filomeni G.**, Lanzetti L., Hamerlik P., Bartolazzi A., Velasco G., Papaleo E., Locatelli F., De Zio D., Maya Mendoza A., Bartek J., Cecconi F. AMBRA1 regulates cyclin D to guard S-phase entry and genomic integrity. ***Nature*** Apr 14. (doi: 10.1038/s41586-021-03422-5) – Online ahead of print.

3. Cirotti C., Rizza S., Giglio P., Poerio N., Allega M.F., Claps G., Lee J-H., Benassi B., Barilà B., Robert C., Stamler J., Cecconi F., Fraziano M., Paull T.T., and **Filomeni G.** (2021) Redox activation of ATM enhances GSNOR translation to sustain mitophagy and tolerance to oxidative stress. ***EMBO Rep.*** 22: e50500.

4. Cirotti C., and **Filomeni G.** (2020) ATM plays antioxidant, boosting mitophagy *via* denitrosylation. ***Autophagy***. 17: 1-3.

5. Rizza S., and **Filomeni G.** (2020) Exploiting *S*-nitrosylation for cancer therapy: facts and perspectives. ***Biochem. J***. 477: 3649-3672.

6. Faienza F., Lambrughi M., Rizza S., Pecorari C., Giglio P., Salamanca Viloria J., Allega M.F., Chiappetta G., Vinh J., Pacello F., Battistoni A., Rasola A., Papaleo E., and **Filomeni G.** (2020) S-nitrosylation affects TRAP1 structure and activity, and modulates cell response to apoptotic stimuli. ***Biochem. Pharmacol.*** 176: 113869.

7. Faienza F., Rizza S., Giglio P., and **Filomeni G.** (2020) TRAP1: A metabolic hub tethering aging to mitochondrial *S*-nitrosylation. ***Frontiers Physiol.*** 11: 340.

8. Rizza S., Di Leo L., Mandatori S., De Zio D., and **Filomeni G.** (2020) Mitophagy contributes to alpha-tocopheryl succinate toxicity in GSNOR-deficient hepatocellular carcinoma. ***Biochem. Pharmacol.*** 176: 113885.

9. Montagna C., Cirotti C., Rizza S., and **Filomeni G.** (2020) When *S*-nitrosylation gets to mitochondria: from signaling to age-related diseases. ***Antioxid. Redox Signal.*** 32: 884-905.

10. Montagna C., Rizza S., Cirotti C., Maiani E., Muscartoli W., Musaró A., Carrí M.T., Ferraro E, Cecconi F., and **Filomeni G.** (2019) nNOS/GSNOR interaction contributes to skeletal muscle differentiation and homeostasis. ***Cell Death Dis.*** 10: 354.

11. Rizza S., and **Filomeni G.** (2018) Role, targets and regulation of (de)nitrosylation in malignancy. ***Front. Oncol.*** 8: 334.

12. Rizza S., and **Filomeni G.** (2018) Denitrosylate and live longer: how GSNOR links mitophagy to aging. ***Autophagy.*** 14: 1285-1287.

13. Rizza S., Cardaci S., Montagna C., Di Giacomo G., De Zio D., Bordi M., Maiani E., Campello S., Borreca A., Puca A.A., Stamler J.S., Cecconi F., and **Filomeni G.** (2018) *S*-nitrosylation drives cell senescence and aging in mammals by controlling mitochondrial dynamics and mitophagy. ***Proc. Natl. Acad. Sci. USA.*** 115: E3388-E3397.

14. Rizza S., and **Filomeni G.** (2017) Chronicles of a reductase: Biochemistry, genetics and physio-pathological role of GSNOR. ***Free Rad. Biol. Med.*** 110: 19-30.

15. Rizza S., Montagna C., Cardaci S., Maiani M., Di Giacomo G., Sanchez-Quiles V., Blagoev B., Rasola A., De Zio D., Stamler J.S., Cecconi F., and **Filomeni G.** (2016) *S*-nitrosylation of the mitochondrial chaperone TRAP1 sensitizes hepatocellular carcinoma cells to succinate dehydrogenase-targeting drugs. ***Cancer Res.*** 76: 4170-4182.

16. Rizza S., and **Filomeni G.** (2017) Tumor suppressor roles of the denitrosylase GSNOR. ***Crit. Rev. Oncog.*** 21: 433-445.

17. Montagna C., Rizza S., Maiani E., Piredda L., **Filomeni G**., and Cecconi F. (2016) To eat, or NOt to eat: *S*-nitrosylation signaling in autophagy. ***FEBS J.*** Apr 15. 283: 3857-3869.

18. Rizza S., Cirotti C., Montagna C., Cardaci S., Consales C., Cozzolino M., Carrí M.T., Cecconi F., and **Filomeni G**. (2015) *S*-nitrosoglutathione reductase plays opposite roles in SH-SY5Y models of Parkinson's disease and amyotrophic lateral sclerosis. ***Mediators Inflamm.*** 2015: 536238.

19. **Filomeni G**., De Zio D., and Cecconi F. (2014) Oxidative stress and autophagy: the clash between damage and metabolic needs. ***Cell Death Differ.*** 2014 22: 377-388.

20. Montagna C., Di Giacomo G., Rizza S., Cardaci S., Ferraro E., Grumati P., De Zio D., Maiani E., Muscoli C., Lauro F., Ilari S., Bernardini S., Cannata S., Gargioli C., Ciriolo M.R., Cecconi F., Bonaldo P., and **Filomeni G.** (2014) *S*-nitrosoglutathione reductase deficiency-induced *S*-nitrosylation results in neuromuscular dysfunction. ***Antioxid. Redox Signal.*** 21: 570-587.