

**BIOGRAPHICAL SKETCH**

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NAME: SIMONE SABBIONEDA

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

POSITION TITLE: FIRST RESEARCHER

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<br>(if applicable) | Completion Date<br>MM/YYYY | FIELD OF STUDY                    |
|------------------------------------------------------------------------|---------------------------|----------------------------|-----------------------------------|
| Università Degli Studi di Milano, MI, Italy                            | BSc                       | 10/2001                    | Cell cycle control                |
| Università Degli Studi di Milano, MI, Italy                            | PhD                       | 12/2004                    | DNA damage response and tolerance |
| Genome Damage and Stability Centre, University of Sussex, Brighton, UK |                           | 08/2005-10/2011            | DNA damage response and tolerance |

**A. Personal Statement**

Since my formation years I always have been interested in the control of DNA replication and genome stability. I fuelled this desire by planning the growth of my scientific career during my postdoctoral fellowship first and even more after moving to IGM to open my own lab. I always focused on the control of DNA translesion synthesis a topic that merges those two interconnecting interests, focusing mainly on DNA polymerase  $\eta$ . During my scientific peregrinations I was able to unravel some of the mechanisms that control this important polymerase, and I am one of the outmost experts in its post translational modifications in human cells.

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

2023-2025 PRIN 2022 - " Unconventional roles of polymerase eta in the maintenance of genome stability"  
2021-2025 AIRC Investigator Grant 24316- "Spatio-temporal regulation of translesion synthesis and its implication for damage bypass and acquired chemoresistance"  
2019-2021 PRIN 2017 – Unit Leader in the Project “G quadruplexes as modulators of genome stability”

**B. Positions, Scientific Appointments, and Honors**

2023-current First Researcher, Istituto di Genetica Molecolare, CNR, Pavia  
2011-2022 Researcher, Istituto di Genetica Molecolare, CNR, Pavia  
2012-current Manager of Imaging and Sorting facilities of Istituto di Genetica Molecolare, CNR, Pavia  
2022-2034 National Scientific Qualification for Full Professor (Level I) for sector 05/I1 (Genetics)  
2017-2029 National Scientific Qualification for Assistant Professor (Level II) for sectors 05/E2 (Molecular Biology) and 05/I1 (Genetics)  
2012-current Proponent of the PhD course in Genetica, Biologia Molecolare e Cellulare, University of Pavia

## C. Contributions to Science

1) Identification and characterization of post translational modifications of TLS polymerases. He was among the first to describe the phosphorylation of two TLS polymerases, Rev1 and pol $\eta$  in two different organisms and he was instrumental in the study of the role of ubiquitylation of pol $\eta$  in human cells. The discovery of PTMs of TLS components shed more light on the molecular mechanisms of one of the cells most important tolerance pathways that prevents increased mutagenesis and genetic instability, one of the hallmarks of cancer.

- a. Simone Sabbioneda, Ileana Bortolomai, Michele Giannattasio, Paolo Plevani, Marco Muzi Falconi. Yeast Rev1 is cell cycle regulated, phosphorylated in response to DNA damage and its binding to chromosomes is dependent upon MEC1. *Dna Repair* (2007) Jan 4;6(1):121-7.
- b. Bienko M, Green CM, Sabbioneda S, Crosetto N, Matic I, Hibbert RG, Begovic, T, Niimi A, Mann M, Lehmann AR, Dikic I. Regulation of translesion synthesis DNA polymerase  $\eta$  by monoubiquitination (2010) *Mol Cell*. Feb 12;37(3):396-407.
- c. Sabbioneda S, Green CM, Bienko M, Kannouche P, Dikic I, Lehmann AR. Ubiquitin-binding motif of human DNA polymerase  $\eta$  is required for correct localization. (2009) *Proc Natl Acad Sci U S A*. Feb 24;106(8):E20
- d. Göhler T, Sabbioneda S, Green CM, Lehmann AR. ATR-mediated phosphorylation of DNA polymerase  $\eta$  is needed for efficient recovery from UV damage. (2011) *J Cell Biol*. Jan 24;192(2):219-27

2) Establishing a connection between DNA damage checkpoint and Translesion Synthesis. Tightly linked to the discovery of the phosphorylation of TLS players was the finding of the cross talk between damage tolerance and DNA damage checkpoint, both in yeast and in human cells.

- a. Simone Sabbioneda, Brenda Minesinger, Michele Giannattasio, Paolo Plevani, Marco Muzi Falconi, Sue Jinks-Robertson. The 9-1-1 Checkpoint Clamp Physically Interacts with Pol $\xi$  and Is Partially Required for Spontaneous Pol $\xi$ -dependent Mutagenesis in *Saccharomyces cerevisiae*. (2005) *J. Biol. Chem*. 280, 38657-65
- b. Göhler T, Sabbioneda S, Green CM, Lehmann AR. ATR-mediated phosphorylation of DNA polymerase  $\eta$  is needed for efficient recovery from UV damage. (2011) *J Cell Biol*. Jan 24;192(2):219-27

3) Discovery of new regulatory mechanisms that control pol  $\eta$  stability during the cell cycle and its recruitment to chromatin. The identification of this kind of regulation will hopefully allow designing better strategies for its inhibition in chemotherapeutic resistant cancer cells.

- a. Bertoletti F, Cea V, Liang CC, Lanati T, Maffia A, Avarello MDM, Cipolla L, Lehmann AR, Cohn MA, Sabbioneda S. Phosphorylation regulates human pol $\eta$  stability and damage bypass throughout the cell cycle. (2017) *Nucleic Acids Res*. Sep 19;45(16):9441-9454. doi: 10.1093/nar/gkx619.
- b. Sabbioneda S, Gourdin AM, Green CM, Zotter A, Giglia-Mari G, Houtsmuller A, Vermeulen W, Lehmann AR. Effect of proliferating cell nuclear antigen ubiquitination and chromatin structure on the dynamic properties of the Y-family DNA polymerases. (2008) *Mol Biol Cell*. Dec;19(12):5193-202.
- c. Cipolla L, Bertoletti F, Maffia A, Liang CC, Lehmann AR, Cohn MA, Sabbioneda S. UBR5 interacts with the replication fork and protects DNA replication from DNA polymerase  $\eta$  toxicity. (2019) *Nucleic Acids Res*. Oct 5. pii: gkz824. doi: 10.1093/nar/gkz824.

4) Development of a fast and efficient experimental framework to characterise Variant of Uncertain Significance (VUS) of pol $\eta$ , providing diagnostic confirmation for genetic counselling.

- a. Ricciardiello R, Forleo G, Cipolla L, van Winckel G, Marconi C, Nospikel T, Halazonetis TD, Zgheib O, Sabbioneda S. Homozygous substitution of threonine 191 by proline in polymerase  $\eta$  causes Xeroderma pigmentosum variant. *Sci Rep*. 2024 Jan 11;14(1):1117. doi: 10.1038/s41598-023-51120-1.

#### D. Publications

Secchi M, Garbelli A, Riva V, Deidda G, Santonicola C, Formica TM, Sabbioneda S, Crespan E, Maga G. Synergistic action of human RNaseH2 and the RNA helicase-nuclease DDX3X in processing R-loops. *Nucleic Acids Res*. 2024 Oct 28;52(19):11641-11658. doi: 10.1093/nar/gkaf731.

Zamperla MG, Illi B, Barbi V, Cencioni C, Santoni D, Gagliardi S, Garofalo M, Zingale GA, Pandino I, Sbardella D, Cipolla L, Sabbioneda S, Farsetti A, Ripamonti C, Fossati G, Steinkühler C, Gaetano C, Atlante S. HDAC6 inhibition disrupts HDAC6-P300 interaction reshaping the cancer chromatin landscape. *Clin Epigenetics*. 2024 Aug 18;16(1):109. doi: 10.1186/s13148-024-01725-8.

Boufaied N, Chetta P, Hallal T, Cacciatore S, Lalli D, Luthold C, Homsy K, Imada EL, Syamala S, Photopoulos C, Di Matteo A, de Polo A, Storaci AM, Huang Y, Giunchi F, Sheridan PA, Michelotti G, Nguyen QD, Zhao X, Liu Y, Davicioni E, Spratt DE, Sabbioneda S, Maga G, Mucci LA, Ghigna C, Marchionni L, Butler LM, Ellis L, Bordeleau F, Loda M, Vaira V, Labbé DP, Zadra G.

Obesogenic High-Fat Diet and MYC Cooperate to Promote Lactate Accumulation and Tumor Microenvironment Remodeling in Prostate Cancer. *Cancer Res*. 2024 Jun 4;84(11):1834-1855. doi: 10.1158/0008-5472.CAN-23-0519.

Cardano M, Magni M, Alfieri R, Chan SY, Sabbioneda S, Buscemi G, Zannini L. Sex specific regulation of TSPY-Like 2 in the DNA damage response of cancer cells. *Cell Death Dis*. 2023 Mar 15;14(3):197.

Zardoni L, Nardini E, Brambati A, Lucca C, Choudhary R, Loperfido F, Sabbioneda S, Liberi G. Elongating RNA polymerase II and RNA:DNA hybrids hinder fork progression and gene expression at sites of head-on replication-transcription collisions. *Nucleic Acids Res*. 2021 Dec 16;49(22):12769-12784.

Mentegari E, Bertoletti F, Kissova M, Zucca E, Galli S, Tagliavini G, Garbelli A, Maffia A, Bione S, Ferrari E, Fagagna FDD, Francia S, Sabbioneda S, Chen LY, Lingner J, Bergoglio V, Hoffmann JS, Hübscher U, Crespan E, Maga G. A Role for Human DNA Polymerase  $\lambda$  in Alternative Lengthening of Telomeres. *Int J Mol Sci*. 2021 Feb 27;22(5):2365.

Cabrini M, Roncador M, Galbiati A, Cipolla L, Maffia A, Iannelli F, Sabbioneda S, d'Adda di Fagagna F, Francia S. DROSHA is recruited to DNA damage sites by the MRN complex to promote non-homologous end joining. *J Cell Sci*. 2021 Mar 22;134(6):jcs249706.

Riva V, Garbelli A, Casiraghi F, Arena F, Trivisani CI, Gagliardi A, Bini L, Schroeder M, Maffia A, Sabbioneda S, Maga G. Novel alternative ribonucleotide excision repair pathways in human cells by DDX3X and specialized DNA polymerases. *Nucleic Acids Res*. 2020 Nov 18;48(20):11551-11565. doi: 10.1093/nar/gkaa948.

Maffia A, Ranise C, Sabbioneda S. From R-Loops to G-Quadruplexes: Emerging New Threats for the Replication Fork (2020). *Int J Mol Sci*. Feb 22;21(4). pii: E1506. doi: 10.3390/ijms21041506

Belloni E, Di Matteo A, Pradella D, Vacca M, Wyatt CDR, Alfieri R, Maffia A, Sabbioneda S, Ghigna C. Gene Expression Profiles Controlled by the Alternative Splicing Factor Nova2 in Endothelial Cells. (2019) *Cells*. Nov 23;8(12). pii: E1498. doi: 10.3390/cells8121498.

González Besteiro MA, Calzetta NL, Loureiro SM, Habif M, Bétous R, Pillaire MJ, Maffia A, Sabbioneda S, Hoffmann JS, Gottifredi V. Chk1 loss creates replication barriers that compromise cell survival independently of excess origin firing. (2019) *EMBO J*. Aug 15;38(16):e101284. doi: 10.15252/embj.2018101284.

Besio R, Garibaldi N, Leoni L, Cipolla L, Sabbioneda S, Biggiogera M, Mottes M, Aglan M, Otaify GA, Temtamy SA, Rossi A, Forlino A. Cellular stress due to impairment of collagen prolyl hydroxylation complex is rescued by the chaperone 4-phenylbutyrate. (2019) *Dis Model Mech*. Jun 20;12(6). pii: dmm038521. doi: 10.1242/dmm.038521

Besio R, Iula G, Garibaldi N, Cipolla L, Sabbioneda S, Biggiogera M, Marini JC, Rossi A, Forlino A. 4-PBA ameliorates cellular homeostasis in fibroblasts from osteogenesis imperfecta patients by enhancing autophagy and stimulating protein secretion. (2018) *Biochim Biophys Acta Mol Basis Dis*. May;1864(5 Pt A):1642-1652.

Mentegari E, Crespan E, Bavagnoli L, Kissova M, Bertoletti F, Sabbioneda S, Imhof R, Sturla SJ, Nilforoushan A, Hübscher U, van Loon B, Maga G. Ribonucleotide incorporation by human DNA polymerase  $\eta$  impacts translesion synthesis and RNase H2 activity. (2017) *Nucleic Acids Res*. Mar 17;45(5):2600-2614.

Cipolla L, Maffia A, Bertoletti F, Sabbioneda S. The Regulation of DNA Damage Tolerance by Ubiquitin and Ubiquitin-Like Modifiers. (2016) *Front Genet*. Jun 13;7:105

Kanu N, Zhang T, Burrell RA, Chakraborty A, Cronshaw J, DaCosta C, Grönroos E, Pemberton HN, Anderton E, Gonzalez L, Sabbioneda S, Ulrich HD, Swanton C, Behrens A. RAD18, WRNIP1 and ATMIN promote ATM signalling in response to replication stress. (2016) *Oncogene*. Jul 28;35(30):4020

Harley ME, Murina O, Leitch A, Higgs MR, Bicknell LS, Yigit G, Blackford AN, Zlatanou A, Mackenzie KJ, Reddy K, Halachev M, McGlasson S, Reijns MA, Fluteau A, Martin CA, Sabbioneda S, Elcioglu NH, Altmüller J, Thiele H, Greenhalgh L, Chessa L, Maghnie M, Salim M, Bober MB, Nürnberg P, Jackson SP, Hurles ME, Wollnik B, Stewart GS, Jackson AP. TRAIP promotes DNA damage response during genome replication and is mutated in primordial dwarfism. (2016) *Nat Genet*. Jan;48(1):36-43.

Zlatanou A, Sabbioneda S, Miller ES, Greenwalt A, Aggathangelou A, Maurice MM, Lehmann AR, Stankovic T, Reverdy C, Colland F, Vaziri C, Stewart GS. USP7 is essential for maintaining Rad18 stability and DNA damage tolerance. (2016) *Oncogene*. Feb 25;35(8):965-76

Cea V, Cipolla L, Sabbioneda S. Replication of Structured DNA and its implication in epigenetic stability. (2015) *Front Genet*. Jun 16;6:209

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Simone Sabbioneda, Lisa di Nola, Federico Lazzaro, Marco Muzi Falconi, Paolo Plevani. The DNA damage checkpoint response in budding yeast. (2004) *Recent development in nucleic acid research*.

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