PHYSICIAN SCIENTIST
LA MEDICINA INCONTRA LA RICERCA
promosso da: AIRC Fondazione CARIPLO | con il supporto di: SEMM UNIVERSITÀ DEGLI STUDI DI MILANO

2026 Physician Scientist Call

AVAILABLE POSITIONS

Principal Investigator	**MUZI FALCONI MARCO**
Institute of Affiliation	Università degli Studi di Milano
Title of the proposed project:	A novel gene modulating genomic instability in cancer cells: mechanisms and functions in chromatin regulation
Short description of the project	Transcription-replication conflicts and genome instability are major vulnerabilities of cancer cells. Non-canonical nucleic acid structures, including R-loops and G-quadruplexes, are important sources of these conflicts because they can obstruct DNA replication and repair. They impair replication fork progression, promote DNA damage, and contribute to mutations and chromosomal rearrangements. G-quadruplexes are enriched in regulatory regions, oncogenes, repetitive sequences, and telomeres, where they can induce replication stress and genome fragility. We recently identified in human cells a putative orthologue of Saccharomyces cerevisiae Vid22, a G4-binding protein. Both proteins contain conserved BED and RNase H-like domains, suggesting an evolutionarily conserved role in nucleic acid metabolism. Mass spectrometry analysis of proteins interactors identified several crucial chromatin regulators. Loss of the Vid22 orthologue leads to micronuclei formation, increased MYC and KRAS expression, deregulation of inflammatory pathways, and altered expression of histone genes, supporting its role in genome and chromatin homeostasis. This project will test the hypothesis that the human orthologue of Vid22 protects cancer-relevant genomic regions from G4- and R-loop-associated instability by coordinating chromatin remodeling, transcription, replication, DNA repair, and checkpoint signaling. We will define how it functionally interacts with chromatin remodellers to control replication stress responses and transcription-replication conflicts. By combining molecular, genomic, and cellular approaches, the PhD student will determine whether this novel human gene acts as a guardian of difficult-to-replicate genomic regions and will clarify how its dysfunction contributes to cancer-associated genome instability. The proposed work links mechanistic cancer biology to clinically relevant questions on genome maintenance, oncogene activation, inflammatory signaling, and potential therapeutic vulnerabilities. The Department of Biosciences, University of Milano, offers access to all the relevant facilities and an international and scientifically stimulating environment. The PhD student will be supported by a senior lab member and will be trained in state of the art molecular biology and genomics approaches.
Main research area for the project	Molecular biology
5 keywords for the project	DNA damage - Genomic/Genetic instability - Chromatin remodeling - Translesion synthesis - DNA replication

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LAB INFO	
Main topic/s of the lab	Mechanisms controlling genome stability in human and cancer cells
Short description of the lab activity	The laboratory focuses on the molecular mechanisms that preserve genome integrity, in normal and cancer cells, with particular emphasis on DNA replication and DNA repair pathways. Defects in these processes are directly linked to tumorigenesis and to the onset of several genetic disorders. Most chemotherapeutics approaches exploit the deregulation of these pathways observed cancer cells to achieve preferential killing of the same cancer cells. In recent years, a major line of research in the laboratory has been the characterization of a novel Saccharomyces cerevisiae gene involved in the maintenance of genome stability, particularly at genomic regions prone to forming G-quadruplex DNA secondary structures. This gene was identified through a genetic screen in yeast. Building on these findings, we are now investigating its putative human orthologue. The best candidate identified so far is also implicated in the maintenance of chromosomal integrity, and ongoing work is aimed at defining its functional role and its possible connection with G-quadruplex-associated genome instability and the 3D organization of the nuclear genome. The laboratory has also long-standing expertise in the study of DNA damage responses triggered by UV-induced DNA lesions and related genotoxic insults. In this context, we investigate the links between DNA repair pathways and the activation of DNA damage checkpoints mediated by ATM and ATR kinases, which control cell proliferation when facing genotoxic insults. Another research interest concerns the consequences of ribonucleotide incorporation into genomic DNA. We study how embedded ribonucleotides affect chromosome stability, replication fidelity and mitotic chromosome segregation and how they impact the innate immune response and triggering of an inflammatory response. This work is supported by the use of advanced genomic approaches, including third-generation Nanopore sequencing. Finally, the laboratory is expanding its research interests to the study of Haspin kinase and its role in modulating cell polarity, and its functional links to autophagy and cell proliferation control.
Recent bibliography	VID22 counteracts G-quadruplex-induced genome instability. NUCLEIC ACIDS RES 2021 Dec; 49: 12785 Roles and regulation of Haspin kinase and its impact on carcinogenesis. CELL SIGNAL 2022 May; 93: 110303 A Haspin-ARHGAP11A axis regulates epithelial morphogenesis through Rho-ROCK dependent modulation of LIMK1-Cofilin. Iscience 2023 Oct; 26: 108011

	Spotlight on G-Quadruplexes: From Structure and Modulation to Physiological and Pathological Roles. INT J MOL SCI 2024 Mar; 25: Detection of ribonucleotides embedded in DNA by Nanopore sequencing. Commun Biol 2024 Apr; 7: 491
Group composition	The research group is composed of a full professor, two associate professors, two senior postdocs (one wet, one bioinformatician), one PhD student, two fellows, two undergraduate students. Two more groups, with related scientific interests and complementary expertises, share the floor and instrumentation, and share weekly lab meetings.
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