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

2026 Physician Scientist Call

AVAILABLE POSITIONS

Principal Investigator	CARETTI GIUSEPPINA
Institute of Affiliation	Università degli Studi di Milano
Title of the proposed project:	The methylate SMYD3 Links Chromosomal Instability to the Cytosolic DNA Sensing in Breast Cancer
Short description of the project	Chromosomal instability (CIN) is a hallmark of breast cancer, present in approximately 89% of invasive cases. It plays a critical role in tumor development, disease progression, treatment response, and prognosis. In triple-negative breast cancer (TNBC)-an aggressive subtype lacking classical therapeutic targets-CIN is particularly prevalent and is strongly associated with errors in chromosome segregation during cell division. In triple-negative breast cancer CIN can chronically and pathologically activate pathways that sustain enhanced survival and growth of cancer cells through different signaling pathways, such as STAT3 and non-canonical NF-κB. SMYD3 is an epigenetic factor that adds methyl groups to histone and non-histone proteins. Importantly, it is overexpressed in various cancers, including breast cancer, and contributes to cellular proliferation through the regulation of signaling pathways such as Ras and through control of cell cycle progression. More recently, our group uncovered SMYD3 role in regulating the epithelial-to-mesenchymal transition (EMT)-a process tightly linked to invasiveness and metastasis-as well as its involvement in breast cancer stemness (manuscript submitted). SMYD3 role in multiple cancer-related mechanisms has driven the development of selective inhibitors of its activity, including BCI-121, EPZ031686, and the irreversible inhibitor EM127. These compounds have enabled new preclinical studies with key translational relevance, opening novel avenues to therapeutic strategies targeting SMYD3 in breast cancer. In this PhD project, the candidate will use recently developed inhibitors, advanced imaging techniques, next-generation sequencing, and both in vivo and in vitro approaches to investigate SMYD3 role in chromosomal instability and cancer development. This project offers the candidate the opportunity to gain expertise in epigenetics, cancer biology and next generation sequencing, with direct relevance to the development of new therapeutic approaches for triple-negative breast cancer.
Main research area for the project	Molecular biology
5 key words for the project	Genomic/Genetic instability, Epigenetics, Triple negative breast ca., Aneuploidy, Mitosis

LAB INFO	
Main topic/s of the lab	Epigenetics and transcriptional regulation in cancer
Short description of the lab activity	The first aim is to investigate aneuploidy in cell culture using advanced imaging approaches to characterize chromosomal instability. These findings will be extended to human breast

	cancer (BrCa) specimens by comparing samples with high versus low SMYD3 expression and correlating SMYD3 levels with the degree of aneuploidy in tumor tissues. Past and ongoing collaborations with Prof. L. Ottini (University of Roma La Sapienza) and C. Simone (University of Bari) will support this effort to obtain human specimens. Immunohistochemistry and immunofluorescence analyses will be performed on patient biopsies and mouse tumor samples to validate molecular and cellular alterations, linking SMYD3 expression to aneuploidy-associated phenotypes, disease progression, and tumor aggressiveness. Aim 2 focuses on in vivo studies and single-cell RNA sequencing to map aneuploidy. The PhD candidate will support a postdoctoral researcher in generating BrCa tumor models in which SMYD3 levels and activity are modulated through genetic and pharmacological approaches, in contexts where chromosomal instability is either enhanced or repressed. Tumor growth and progression will be monitored, and collected samples will undergo immunohistochemical analysis. In parallel, single-cell RNA-seq will be performed to define transcriptional profiles at single-cell resolution in the different tumor populations. This work will be carried out in collaboration with Prof. Valentina Proserpio (University of Torino), with support from bioinformatics units at the University of Torino and the University of Milan. The resulting data will be used to infer copy number alterations by linking gene expression patterns to genomic coordinates, allowing quantification of aneuploidy across tumor clones using computational approaches. Additionally, TNBC datasets available on the TCGA platform will be analyzed to stratify patients based on aneuploidy and assess potential associations with SMYD3 and related transcript levels.
Recent bibliography	- DCLK1, a putative novel stem cell marker in human cholangiocarcinoma. HEPATOLOGY 2021 Jan; 73: 144 - Discovery of the 4-aminopiperidine-based compound EM127 for the site-specific covalent inhibition of SMYD3. EUR J MED CHEM 2022 Dec; 243: 114683 - The Lysine Methylase SMYD3 Modulates Mesendodermal Commitment during Development. CELLS-BASEL 2021 May; 10: - Targeting Epigenetic Regulators with HDAC and BET Inhibitors to Modulate Muscle Wasting. INT J MOL SCI 2023 Nov; 24: - Impaired cAMP-PKA-CREB1 signalling drives mitochondrial dysfunction in skeletal muscle during cancer cachexia. NAT METAB 2025 Dec; 7: 2548
Group composition	6 members, including PI. 1 PhD student, 1 junior fellow, 1 post-doc, 2 MSc students
Institutional page link	https://www.unimi.it/it/ugov/person/giuseppina-caretti