

Principal Investigator	PIAZZA ROCCO
Institute of Affiliation	Università degli Studi di Milano – Bicocca
Title of the proposed project:	Towards new therapeutic approaches for the treatment of SETBP1-driven leukemias
Short description of the project	<p>Here is a plain-text draft of approximately 275 words. Towards new therapeutic approaches for the treatment of SETBP1-driven leukemias SETBP1 mutations and deregulated SETBP1 expression are recurrent events in aggressive myeloid malignancies, including myelodysplastic/myeloproliferative neoplasms and acute myeloid leukemia, and are associated with poor clinical outcome. However, the cellular mechanisms through which SETBP1 drives leukemic transformation and therapeutic resistance remain incompletely understood. This PhD project aims to dissect SETBP1-driven leukemogenesis at single-cell resolution and to identify new therapeutic vulnerabilities that could be translated into innovative treatment strategies. The project will combine advanced single-cell technologies, functional genomics and in vivo disease modeling. The PhD student will analyze single-cell transcriptomic and multiomic datasets from human leukemia samples and experimental models to define the cellular states, differentiation blocks and transcriptional programs associated with SETBP1 activation. Particular attention will be given to leukemic stem and progenitor compartments, clonal evolution, inflammatory signaling, epigenetic regulation and interactions with the bone marrow microenvironment. Candidate pathways emerging from computational analyses will be experimentally validated using cellular models, perturbation approaches and molecular assays. A central component of the project will be the development and characterization of mouse models of SETBP1-driven leukemia. These models will be used to investigate disease initiation and progression in vivo, to validate candidate therapeutic targets and to test novel treatment approaches alone or in rational combinations. Integration of mouse model data with human single-cell datasets will allow the identification of conserved disease mechanisms and clinically relevant biomarkers. The candidate will acquire multidisciplinary expertise in leukemia biology, single-cell and spatial technologies, bioinformatic data analysis, and preclinical modeling. Clinical duties, where applicable, could be carried out at the Hematology Unit of the San Gerardo Hospital, Monza, in close connection with the University of Milano-Bicocca.</p>
Main research area for the project	Cancer Biology
5 keywords for the project	Target therapy - Mutation (somatic and/or germline) - Signal transduction inhibitors - Myelodysplastic syndromes (MDS) - Myeloproliferative neoplasms

LAB INFO	
Main topic/s of the lab	Translational hematology, Single-cell and spatial omics.
Short description of the lab activity	<p>The research activity of the laboratory is focused on understanding the molecular mechanisms that drive cancer initiation, progression and therapeutic resistance, with a particular emphasis on hematological malignancies. The laboratory is led by Rocco Piazza, principal investigator and associate professor at the Department of Medicine and Surgery of the University of Milano-Bicocca, Milan. The research group operates at the interface between translational hematology, cancer genomics, computational biology and experimental modeling, taking advantage of the close connection with clinical activities carried out at the Hematology Unit of the San Gerardo Hospital, Monza. A central goal of the laboratory is to identify and functionally characterize genetic and transcriptional alterations responsible for malignant transformation. Over the years, the group has contributed to the discovery and biological characterization of several oncogenic lesions in myeloid and lymphoid malignancies, including SETBP1 and ETNK1 mutations, and has investigated their role in disease pathogenesis, clonal evolution and clinical behavior. These studies provide the conceptual framework for current research programs aimed at translating molecular discoveries into new diagnostic, prognostic and therapeutic strategies. The laboratory combines high-throughput sequencing technologies with wet-lab experimental approaches. Bulk DNA and RNA sequencing are used to identify recurrent genomic lesions, reconstruct clonal architecture and define disease-associated transcriptional programs. More recently, the group has strongly expanded its activity in single-cell and spatially resolved technologies, including single-cell transcriptomics, single-cell multiomics, immune repertoire profiling and spatial transcriptomics. These approaches allow the dissection of tumor heterogeneity at unprecedented resolution, enabling the identification of rare leukemic subpopulations, differentiation trajectories, microenvironmental interactions and cellular states associated with therapy resistance. A major technological asset of the group is the availability of advanced single-cell and spatial platforms, including 10x Genomics Chromium, Chromium X, Visium CytAssist and Xenium systems. These instruments support a wide range of applications, from single-cell whole-transcriptome profiling to multiome analysis, scATAC-seq, spatial transcriptomics and targeted in situ transcript detection. The laboratory also integrates these experimental platforms with dedicated bioinformatic pipelines for data integration and analysis. In parallel, the laboratory develops and applies functional genomics strategies to validate candidate disease drivers and therapeutic vulnerabilities. These include CRISPR-Cas9-based approaches, cellular models, molecular assays and preclinical systems designed to investigate the functional consequences of oncogenic mutations. Particular attention is given to SETBP1-driven leukemias, and the crosstalk</p>

	<p>between tumor cells and the immune microenvironment. Mouse models and patient-derived systems are used to study disease initiation and progression in vivo and to evaluate rational therapeutic strategies. The laboratory activity is therefore highly multidisciplinary, spanning clinical hematology, cancer biology, genomics, single-cell technologies, spatial transcriptomics, computational analysis and experimental validation. This environment offers PhD students the opportunity to acquire a broad and integrated training, from patient-oriented research questions to advanced molecular profiling and preclinical testing. The overall mission is to generate mechanistic knowledge of direct relevance to human disease and to identify innovative approaches for precision medicine in hematological cancers.</p>
Recent bibliography	<p>Clinical relevance of clonal hematopoiesis in persons aged ≥ 80 years. BLOOD 2021 Nov; 138: 2093 Targeting the immune microenvironment in Waldenström Macroglobulinemia via halting the CD40/CD40-ligand axis. BLOOD 2023 May; 141: 2615 The co-evolution of the genome and epigenome in colorectal cancer. NATURE 2022 Nov; 611: 733 First-hit SETBP1 mutations cause a myeloproliferative disorder with bone marrow fibrosis. BLOOD 2024 Apr; 143: 1399 Genetically driven immune microenvironment states associate with therapeutic responses in MYD88 mutant lymphomas. MOL CANCER 2026 Apr;</p>
Group composition	<p>The group is composed of two postdocs in molecular biology, a postdoc in bioinformatics with expertise in omics analysis, a senior technician with in-depth experience in single-cell omics and NGS, two hematology residents and two graduate students, and benefits from the close collaboration of a bioinformatics professor and a biologist with expertise in animal models.</p>
Institutional page link	<p>https://www.medicina.unimib.it/it</p>