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

Principal Investigator	Ficara Francesca
Hosting institution	Humanitas Mirasole S.p.A.
Proposal title	Targeting PBX as a novel therapy for myeloproliferative neoplasm: effect on disease course through innovative assays
Keywords	Drug response and/or resistance; Hematopoiesis; Mouse models; Hematopoietic stem cells; Myeloproliferative neoplasms
PhD project description	Myeloproliferative neoplasms (MPN) are heterogeneous blood malignancies associated with increased risk of leukemic transformation and of inflammation-related thrombotic events. MPN are initiated by somatic mutations occurring in hematopoietic stem and progenitor cells (HSPC) that result in unregulated activation of the JAK/STAT pathway. By exploiting an MPN mouse model, we uncovered a role for the transcription factor PBX1 in driving tumor progression; upon PBX1 genetic inactivation, typical MPN features did not develop or resolved over time, with reversion of the aberrant HSPC transcriptome including downregulation of inflammation-related genes. We are currently exploiting PBX1 as a therapeutic target, taking advantage of the recently developed small molecule T417 that inhibits PBX1 binding to DNA. Preliminary data obtained in our mouse model of MPN indicate that the administration of T417 rescues the thrombocytosis typical of the disease. The aim of the PhD project is to study the effect of T417 on patient's cells through novel xenotransplantation assays and in vitro 3D models that recapitulate the bone marrow microenvironment. Through these tools the candidate will assess if targeting PBX1 dampens the malignant clone, reverts MPN features, and/or resolves inflammation. This research will establish if PBX1 inhibition, compared to or in combination with other treatment modalities, could serve as a novel and more targeted therapy in MPN. While current therapies reduce the risk of adverse events and improve quality of life, they are not curative, leaving unmet clinical needs. This study will provide a proof of principle for using approaches acting at the HSPC level. The project will be carried out at the Humanitas Research Hospital and will take advantage of the local Biobank; the PI is part of the CALR (Center for Accelerating Leukemia/Lymphoma Research) consortium led by Prof. Matteo Della Porta and benefits from daily interactions with the hematologists of the Humanitas Cancer Center.
Main topics of the lab	Myeloid neoplasms; Hematopoietic stem cells
Short description of the lab activity	Our laboratory activities are aimed at studying hematopoietic stem and progenitor cells in physiological and pathological hematopoiesis; we are particularly interested in understanding how the presence of somatic mutations alter the delicate equilibrium between quiescence and activation-differentiation, ultimately leading to hematological disorders. To this purpose, we are studying different aspects

	contributing to preserve stem cell functions including transcription factors, micro-RNAs, cytokines, and interaction with different elements of the bone marrow niche, through multidimensional flow cytometry, different omics, animal models and experiments with primary mouse and patient' cells. Our lab discovered that, within the normal bone marrow, miR-127 is expressed almost exclusively in HSC, where it functions as a brake for myeloid differentiation, contributing to preserve hematopoietic stem cells long-term self-renewal. More recently, we studied hematopoietic stem cells in the context of myeloproliferative neoplasm (MPN), diseases characterized by overproduction of platelets and/or erythroid cells, as a paradigm of hematological diseases initiated by mutated stem cells, to explore novel therapeutic options. We generated a mouse model in which the JAK2-V617F MPN-driver mutation is induced in the absence of the transcription factor PBX1. This tool allowed us to show that PBX1 is a key player in establishing and maintaining MPN, and to identify other potential MPN contributors, which are currently under investigation. In particular, we are interested in molecules expressed in hematopoietic stem cells involved in platelets generation. Moreover, we are exploring the possibility of targeting PBX1 in vivo, thanks to an AIRC-IG grant. To further set our studies in a clinical and translational perspective, we joined Prof. Matteo Della Porta's group in Humanitas Research Hospital, extending our interests to other myeloid disorders such as myelodysplastic syndromes and acute myeloid leukemia, with the aim of dissecting the biological basis of disease onset and progression including immune evasion, and rapidly translate findings of these investigations into clinical tools, combining omics profiling, AI-driven approaches, and molecular studies.
Main research area	Cancer biology
Group composition	The group is composed by 7 members: - Three postdocs, including one bioinformatician - One CNR staff scientist - Three fellows
Institutional page link	https://www.humanitas-research.com/
Lab website link	https://www.humanitas-research.com/researchers/francesca-ficara/
Social media link	https://www.linkedin.com/in/francesca-ficara-346207a
Lab bibliography	PBX1-directed stem cell transcriptional program drives tumor progression in myeloproliferative neoplasm. Muggeo S, Crisafulli L, Uva P, Fontana E, Ubezio M, Morenghi E, Colombo FS, Rigoni R, Peano C, Vezzoni P, Della Porta MG, Villa A, Ficara F STEM CELL REP 2021 Nov; 16: 2607