Principal Investigator	DELLA PORTA MATTEO GIOVANNI
Institute of Affiliation	Università Humanitas
Title of the proposed project:	Functional validation of clonal evolution patterns in myelodysplastic syndromes using bone marrow organoids
Short description of the project	Myelodysplastic syndromes (MDS) are clonal hematopoietic stem cell neoplasms characterized by ineffective hematopoiesis, peripheral cytopenias, and a variable risk of progression to acute myeloid leukemia (AML). These hematologic malignancies represent a unique in vivo model for studying the multistep process of neoplastic transformation of hematopoietic stem cells. In our previous work, we performed longitudinal single-cell multi-omics analyses to define trajectories of clonal evolution from MDS to AML, as well as patterns of treatment response and relapse. While these studies identified distinct evolutionary trajectories of malignant stem and progenitor cells, such observational approaches cannot establish direct causal relationships or fully elucidate how microenvironmental and immune factors drive clonal selection and disease progression. This PhD project aims to functionally validate clonal evolution patterns, treatment responses, and relapse mechanisms using human induced pluripotent stem cell (iPSC)-derived three-dimensional (3D) bone marrow organoids as a controlled experimental platform. The selected candidate will isolate patient-derived clonal hematopoietic cells and engraft them into 3D organoid systems designed to recapitulate the key structural and functional components of the bone marrow niche. Key research responsibilities will include: - Analyzing the functional expansion, persistence, and survival dynamics of malignant stem and progenitor cells within the 3D organoid environment. - Evaluating how specific microenvironmental conditions, including inflammatory and immunoregulatory states, selectively influence clonal trajectories over time. - Testing functional responses to clinically relevant pharmacological treatments to investigate mechanisms of drug resistance and disease relapse. - Integrating functional experimental readouts with single-cell molecular profiles to establish a robust link between descriptive patient-derived data and mechanistic functional validation. The PhD student will carry out his/her clinical and research activities at Humanitas University.
Main research area for the project	Cancer biology
5 key words for the project	Response and/or resistance to therapy, Prognosis, Immune escape, Organoids, Myelodisplastic syndromes (MDS)

LAB INFO	
Main topic/s of the lab	Cancer Genomics and Biology - Artificial Intelligence
Short description of the lab activity	Our lab aims to dissect the mechanisms of disease onset and progression in Hematological Neoplasms, and rapidly translate

	findings of these investigations into clinical tools, combining genomic profiling, AI-driven approaches and molecular studies. 1) Genomics of myeloid neoplasms Myeloid neoplasms (MN, including acute myeloid leukemias, myelodysplastic syndromes and myeloproliferative neoplasms) are rare hematological cancers that include a significant proportion of patients with unmet clinical needs. MN are caused by somatic mutations. These abnormalities may be generated by inherited predispositions, environmental factors, or random mutations arising during DNA replication in normal stem cells. The identification of recurrent genetic events represents one of the most direct approaches to understand cancer biology. Our mission is to study mechanisms of disease in MN, and rapidly translate findings of these investigations into clinical tools within the clinical practice. We combine genomic profiling (RNA/DNA sequencing and innovative single cell analysis) with clinical studies to develop innovative personalized medicine strategies for MN. 2) Artificial Intelligence in hematology We aim to advance the use of artificial intelligence (AI) in hematology. We focus on developing innovative clinical applications of AI and leveraging machine-learning technology in hopes of improving hematological healthcare delivery in areas such as diagnostics, disease prediction and treatment planning. We aim to foster collaboration and communication between physicians, researchers and data-scientists; offer programmatic and technology support for AI initiatives and conduct research in hematological malignancies.
Recent bibliography	- Real-World Validation of Molecular International Prognostic Scoring System for Myelodysplastic Syndromes. J CLIN ONCOL 2023 May; 41: 2827 - Clinical and Genomic-Based Decision Support System to Define the Optimal Timing of Allogeneic Hematopoietic Stem-Cell Transplantation in Patients With Myelodysplastic Syndromes. J CLIN ONCOL 2024 Aug; 42: 2873 - Characterization and Clinical Implications of p53 Dysfunction in Patients With Myelodysplastic Syndromes. J CLIN ONCOL 2025 Jun; 43: 2069 - PU.1-Activated Genomic Regions Define Low-risk MDS Subsets Characterized by Immune Dysregulation and Disease Progression. BLOOD 2026 Jan; : - Molecular-Based Ecosystem to Improve Personalized Medicine in Chronic Myelomonocytic Leukemia. J Clin Oncol 2026 Mar; : JCO2502116
Group composition	Total members 29 - Physician Scientists 7 - Bioinformaticians 3 - Biostatisticians 1 - Molecular Biologists 4 (including 2 PhD students) - Cellular Biologists 3 - Data Scientists 9 - Project Managers 2
Institutional page link	https://www.humanitas-research.com/

Lab website link	https://www.humanitas-research.com/groups/matteo-della-porta-group/