PHYSICIAN SCIENTIST
LA MEDICINA INCONTRA LA RICERCA
promosso da: AIRC Fondazione CARIPLO | con il supporto di: SEMM European School of Molecular Medicine, UNIVERSITÀ DEGLI STUDI DI MILANO

2026 Physician Scientist Call

AVAILABLE POSITIONS

Principal Investigator	**VAGO LUCA ALDO EDOARDO**
Institute of Affiliation	Università Vita-Salute San Raffaele
Title of the proposed project:	Genetic and Epigenetic Trajectories of Immune Escape in Post-Transplant AML Relapse
Short description of the project	Relapse of acute myeloid leukemia (AML) after allogeneic hematopoietic cell transplantation (allo-HCT) remains the principal cause of treatment failure and is largely driven by immune escape from donor-derived immunity. While genetic mechanisms such as HLA loss have been partially elucidated (Vago, NEJM, 2009; Fleischhauer, JCO, 2026; Toffalori, under submission), non-genetic epigenetic routes of immune evasion-including downregulation of HLA class II molecules and upregulation of inhibitory ligands-remain poorly characterized (Toffalori, Nat Med, 2019), particularly regarding their evolutionary origin and clinical determinants. This project aims to define the temporal and mechanistic basis of immune-resistant leukemia variants through integration of clinical metadata, multi-omic profiling, computational modeling, and experimental validation. We hypothesize that distinct relapse modalities arise from specific evolutionary trajectories shaped by intrinsic tumor features and post-transplant exposures, and that epigenetic immune escape frequently emerges de novo under selective pressure. We will analyze AML patients relapsing after allo-HCT using paired longitudinal samples collected at diagnosis and relapse. High-depth whole genome sequencing (WGS), combined with single-cell chromatin accessibility profiling (scATAC-seq), will reconstruct genetic and epigenetic clonal architecture. Building on frameworks developed with Prof. Giulio Caravagna, we will define "epiclones," integrating mutational and chromatin states, and infer their phylogenetic relationships. Coalescent-based modeling will estimate the timing of relapse-initiating clones, distinguishing pre-existing from post-transplant variants. Hierarchical non-negative matrix factorization will identify signatures linked to clinical exposures, which will be validated in vitro using AML cell lines exposed to stimuli that recapitulate clinically relevant conditions.Overall, this project will reconstruct AML relapse evolution and identify molecular signatures enabling risk stratification and personalized relapse prevention strategies.
Main research area for the project	Cancer biology
5 keywords for the project	Leukaemia – Epigenetics - Immune escape - Metabolism/Metabolomics - Hematopoietic stem cell transplantation (HSCT)

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LAB INFO	
Main topic/s of the lab	Leukemia immunobiology after allogeneic hematopoietic cell transplantation
Short description of the lab activity	The Unit has extensive expertise in multi-omics technologies, including WGS, single-cell and spatial omics, supported by long-standing collaborations with leading national and international institutions. These partnerships have enabled the development of advanced genomic and computational approaches and contributed to high-impact publications. In parallel, the laboratory has broad experience in cell-based functional assays to investigate the biological, immunological, and epigenetic consequences of specific perturbations.
Recent bibliography	Integrated Multiomic Profiling Identifies the Epigenetic Regulator PRC2 as a Therapeutic Target to Counteract Leukemia Immune Escape and Relapse. CANCER DISCOV 2022 Jun; 12: 1449 Phase II trial of hypomethylating agent combined with nivolumab for acute myeloid leukaemia relapse after allogeneic haematopoietic cell transplantation-Immune signature correlates with response. BRIT J HAEMATOL 2023 Oct; 203: 264 Tricking the Trickster: Precision Medicine Approaches to Counteract Leukemia Immune Escape after Transplant. BLOOD 2024 Jun; 143: 2710 Clinical application of tumour-in-normal contamination assessment from whole genome sequencing. Nat Commun 2024 Jan; 15: 323 Donor Selection and Human Leukocyte Antigen Loss Leukemia Relapse After Hematopoietic Cell Transplantation. J CLIN ONCOL 2026 Jun; : JCO2600113
Group composition	Total members: 11 Team composition: 1 Group Leader (PI of the AIRC Investigator Grant), 1 Research Assistant, 1 Senior Postdoctoral Researcher, 1 Senior Bioinformatician, 3 PhD students with a medical degree (including 2 physicians specialized in Hematology), 2 graduate students, 2 undergraduate students, and 2 laboratory technicians.Core expertise: cancer genomics and epigenomics, immunology, molecular and cellular biology, bioinformatics, preclinical mouse models, and translational leukemia research.
Institutional page link	https://research.hsr.it/en/divisions/immunology-transplantation-and-infectious-diseases/immunogenetics-leukemia-genomics-immunobiology/luca-vago.html