

 <p>UniSR Università Vita-Salute San Raffaele</p>	<p>APPLICATION TO ACT AS SUPERVISOR AND RESEARCH PROJECT PROPOSAL</p>	<p>MO 20-5 ed. 02 of 16/01/2026 PO 20 Page 5 of 8</p>
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PROJECT

Supervisor: Luca Aldo Edoardo Vago

Title: Dissection of genetic and epigenetic clonal evolution to identify new clinical determinants of post-transplantation leukemia relapse

Curriculum: Gene and Cell Therapy

Link to the personal page of the University or relevant hospital site website: <https://research.hsr.it/en/divisions/immunology-transplantation-and-infectious-diseases/immunogenetics-leukemia-genomics-and-immunobiology.html>

Description of the Project (max 3,000 characters including spaces)

Background/gap of knowledge

Acute myeloid leukemia (AML) relapse after allogeneic hematopoietic cell transplantation (allo-HCT) remains the main cause of post-transplant failure¹, largely driven by immune-escape from donor immunity.²⁻⁶ Defining both the mechanisms and the evolutionary timing of resistance is essential to identify vulnerable phases of tumor adaptation and opportunities for prevention.⁷ Recent studies on genomic HLA loss relapses have shown that allo-HCT is a complex selective system in which not only immune pressure but also transplant-associated exposures—such as antiviral therapies—can influence the emergence of resistant clones (*Toffalori, under submission*). However, while genetic immune-escape mechanisms have begun to be dissected, non-genetic, epigenetic forms of relapse—such as HLA class II silencing or upregulation of inhibitory ligands—remain poorly characterized, and it is unknown whether resistant clones pre-exist or arise post-transplant, or which exposures drive their selection. Clarifying timing, origin, and drivers of epigenetic escape is crucial for precision-guided post-transplant strategies.

Rationale and hypothesis

Relapse post-allo-HCT is not random but follows mutually exclusive immune-escape trajectories: (i) genomic HLA loss events and (ii) epigenetic mechanisms such as downregulation of HLA class II molecules or upregulation of inhibitory ligands. We hypothesize that these relapse modalities are shaped by distinct genetic and epigenetic evolutionary programs influenced by transplant variables and post-transplant clinical exposures. By integrating multi-omic profiling of leukemic cells with high-resolution clinical metadata, we aim to reconstruct the evolutionary

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paths of relapse-initiating clones, identify early predictors of their selection, and uncover actionable molecular signatures to inform tailored intervention strategies.

Objectives and specific aims

1. Characterize the genetic and epigenetic clonal landscape of AML relapse after allo-HCT
2. Reconstruct evolutionary trajectories and timing of relapse initiating clones
3. Identify mutational and chromatin-based signatures linked to clinical exposures

Expected outcomes

By integrating evolutionary timing, chromatin-state profiling, and granular clinical data, this project will clarify whether post-transplant events primarily select pre-existing variants or actively drive the emergence of resistant epiclones. The identification of mutational and epigenetic signatures linked to specific exposures will illuminate mechanistic contributors to clonal evolution and immune escape. Analyses of pre-treatment samples may further reveal early eco-evolutionary cues predictive of relapse modality, enabling more precise risk stratification and targeted surveillance.

Skills that the student should acquire (max. 600 characters including spaces):

The student will develop an integrated set of wet-lab and computational competencies. They will work with primary AML samples and cell lines, acquiring proficiency in WGS and scATAC-seq library preparation as well as in functional assays to assess epigenetic effects of clinically relevant exposures. In parallel, they will build strong bioinformatic and programming skills for data processing, multi-omic integration, and evolutionary analysis. This combined training will provide robust interdisciplinary expertise in genomics and epigenetics within a translational clinical framework.

References (max. 15)

1. Spellman SR, Xu K, Oloyede T, Ahn KW, Akhtar O, Bolon Y-T, et al. Current Activity Trends and Outcomes in Hematopoietic Cell Transplantation and Cellular Therapy - A Report from the CIBMTR. *Transplant Cell Ther.* 2025;31:505-32
2. Zeiser R, Vago L. Mechanisms of immune escape after allogeneic hematopoietic cell transplantation. *Blood* 2019;133(12):1290-7
3. Vago L, Perna SK, Zanussi M, Mazzi B, Barlassina C, Stanghellini MTL, et al. Loss of mismatched HLA in leukemia after stem-cell transplantation. *N Engl J Med.* 2009;361:478-88.
4. Christopher MJ, Petti AA, Rettig MP, Miller CA, Chendamara E, Duncavage EJ, et al. Immune Escape of Relapsed AML Cells after Allogeneic Transplantation. *N Engl J Med.* 2018;379:2330-41.
5. Toffalori C, Zito L, Gambacorta V, Riba M, Oliveira G, Bucci G, et al. Immune signature drives leukemia escape and relapse after hematopoietic cell transplantation. *Nat Med.* 2019;25:603-11.
6. Gambacorta V, Beretta S, Ciccimarra M, Zito L, Giannetti K, Andrisani A, et al. Integrated Multiomic Profiling Identifies the Epigenetic Regulator PRC2 as a Therapeutic Target to Counteract Leukemia Immune Escape and Relapse. *Cancer Discov.* 2022;12:1449-61.
7. Soragni A, Knudsen ES, O'Connor TN, et al. Acquired resistance in cancer: towards targeted therapeutic strategies. *Nat Rev Cancer* 2025;25(8):613-33.