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	SERAFINI MARTA
Institute of Affiliation	Fondazione M. Tettamanti M. De Marchi Onlus
Title of the proposed project:	Multifunctional CARs for enhanced leukemic stem cell targeting and bone marrow homing
Short description of the project	Therapeutic resistance and relapse in AML are largely driven by leukemic stem cells (LSCs), which persist within the protective bone marrow (BM) niche after standard therapies. To address these barriers, we aim to develop multifunctional next-generation CAR T cells that combine LSC-directed dual-antigen targeting with enhanced BM homing to achieve more effective elimination of LSCs within their niche. We have previously engineered dual-targeting CARs using the IF-BETTER strategy to simultaneously recognize CD33 and the LSC-associated marker TIM-3, by pairing a second-generation CAR with a cytokine-costimulatory receptor (CCR). These constructs showed potent, antigen-restricted cytotoxicity against AML cell lines and primary blasts, including LSCs, while sparing normal immune and hematopoietic cells (doi10.64898/2026.04.22.719217). In parallel, forced CXCR4 expression in conventional CD33CARs improved BM homing, eradication of BM-resident leukemia, and survival in AML xenografts (doi10.1182/blood.2022018330). This project will integrate these features into tricistronic TIM-3/CD33CAR-CXCR4 constructs and evaluate them in vitro and in vivo. We will use Cytokine-Induced Killer (CIK) cells (doi:10.1182/blood-2011-02-336321) non-virally engineered with Sleeping Beauty (SB) transposon system to express multifunctional CARs. These effector cells and the gene transfer platform have been already tested clinically by our group in relapsed ALL after HSCT with CD19.CAR-redirected CIK cells, demonstrating the safety and efficacy of this strategy (doi:10.1172/JCI138473). TIM-3/CD33CAR-CXCR4 CIK cells will be evaluated in vitro for antigen specificity, cytotoxicity, cytokine production, proliferation, exhaustion marker expression, and CXCR4-dependent chemotaxis. In vivo efficacy will be tested in established AML cell line and patient-derived xenograft (PDX) models using dual-luciferase tracking and multiparametric flow cytometry. Residual LSCs will be quantified by flow cytometry and by limiting-dilution secondary/tertiary transplantation into NSG recipients. Finally, a humanised ossicle model will be used to assess TIM-3/CD33CAR-CXCR4 CIK cell infiltration and LSC clearance within a physiologically relevant human stromal BM microenvironment (doi10.1016/j.scr.2014.01.006).
Main research area for the project	Cancer Biology
5 keywords for the project	Cancer stem cells - Acute Myeloid Leukemia (AML) – Microenvironment - CAR engineered cells

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LAB INFO	
Main topic/s of the lab	Leukemia, CAR engineered cells, microenvironment
Short description of the lab activity	The research activities will be conducted at the Tettamanti Research Center, part of the Pediatric Clinic of Fondazione IRCCS San Gerardo dei Tintori in Monza (www.fondazionetettamanti.it). This centre is a leading institution in pediatric hematology-oncology and translational immunotherapy, with longstanding expertise in non-viral CAR-CIK engineering using the Sleeping Beauty transposon system. The Center hosts dedicated facilities for molecular biology, cellular immunology, and translational hematology. Available resources include a large biobank of cryopreserved AML patient samples, advanced flow cytometry platforms (BD FACSAria I, FACSCanto II, LSRFortessa X-20 and Cytek Aurora spectral cytometer), a Seahorse XF Pro Analyzer for metabolic studies, an Operetta CLS high-content imaging system, an Incucyte Live-Cell Analysis System, a Luminex FLEXMAP 3D platform, and access to 10x Genomics single-cell RNA sequencing, CyTOF, and proteomic analyses. The research will also benefit from the University of Milano-Bicocca's pathogen-free animal facility, located in a building adjacent to the Tettamanti Research Center. An in-house GMP Cell Factory, authorized by AIFA, supports the manufacturing and quality control of cell therapy medicinal products for clinical application, thereby providing a direct bridge from research to clinical translation. The intellectual environment is further enriched by other externally funded researchers working on childhood hematological disorders, fostering a strong atmosphere of collaboration and innovation. The PhD student may also carry out clinical activities at the Pediatric Clinic of the Milano-Bicocca Medical School, located at the Fondazione IRCCS San Gerardo dei Tintori in Monza. Altogether, these resources provide a scientifically robust environment for the research, treatment, and cure of childhood hematological disorders, strongly supporting the proposed research and its successful completion.
Recent bibliography	Catch me if you can: how AML and its niche escape immunotherapy. LEUKEMIA 2022 Jan; 36: 13 Selective homing of CAR-CIK cells to the bone marrow niche enhances control of the Acute Myeloid Leukemia burden. BLOOD 2023 May; 141: 2587 Engineering tandem CD33xCD146 CAR CIK (cytokine-induced killer) cells to target the acute myeloid leukemia niche. Front Immunol 2023; 14: 1192333 Optimized GMP-grade production of non-viral Sleeping Beauty-generated CARCIK cells for enhanced fitness and clinical scalability. J TRANSL MED 2025 May; 23: 559 IL-3-zetakine combined with a CD33 costimulatory receptor as a dual CAR approach for safer and selective targeting of AML. Blood Adv 2023 Jun; 7: 2855
Group composition	The group led by Prof. Serafini currently consists of nine members: one project leader, three postdoctoral researchers, three PhD students, and two master's students.

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Institutional page link	https://fondazionetettamanti.it
Lab website link	https://fondazionetettamanti.it/centro-di-ricerca