PHYSICIAN SCIENTIST
LA MEDICINA INCONTRA LA RICERCA
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Principal Investigator	Roti Giovanni
Hosting institution	Università degli Studi di Parma
Proposal title	Dissecting ETP-ALL Vulnerabilities Via Single-Cell Genomics and Ex Vivo Drug Response Profiling
Keywords	Acute Lymphoblastic Leukemia (ALL); Kinase/Kinome; Small molecule inhibitors; Signal transduction inhibitors; Artificial intelligence
PhD project description	Early T-cell precursor acute lymphoblastic leukemia (ETP-ALL) is a high-risk subtype of T-ALL marked by stem-like properties, multilineage transcriptional programs, and resistance to conventional chemotherapy. ETP-ALL cells co-express lymphoid and myeloid gene signatures and lack definitive immunophenotypic markers, making them challenging to classify and treat using standard genomic-guided approaches. As such, there is an urgent need to identify new therapeutic vulnerabilities, particularly in the relapsed/refractory setting. This project aims to define actionable treatment strategies for ETP-ALL through the integration of ex vivo drug response profiling (DRP) with single-cell multi-omic characterization. We have assembled a unique cohort of 30 primary ETP-ALL patient samples, for which we have generated high-resolution single-cell RNA-seq and ATAC-seq data, along with comprehensive ex vivo drug sensitivity profiles across nearly 200 targeted and investigational compounds. By integrating these datasets, we aim to map drug sensitivities to specific transcriptional states, chromatin accessibility patterns, and leukemic subpopulations. This approach will allow us to uncover functional dependencies and pharmacologic vulnerabilities that are not evident from bulk genomics alone. Our preliminary data suggest that ETP-ALL cells are selectively sensitive to BCL-2 and MCL-1 inhibition. Through this platform, we will validate and expand these observations in a patient-specific and mechanistically informed manner. In parallel, ongoing DRP profiling linked to national clinical studies at the Hematology and BMT Unit of the University of Parma enables rapid clinical translation. This includes the implementation of individualized, N-of-1 therapeutic strategies based on ex vivo responses. Ultimately, we aim to construct predictive models that link chromatin states, gene expression programs, and drug sensitivities to support a dynamic, systems-level precision medicine framework. Our goal is to improve therapeutic outcomes for patients with ETP-ALL by enabling biology-driven treatment decisions, particularly in genomically uninformative or treatment-resistant cases.
Main topics of the lab	Genomics of Acute Leukemia | High throughput screening| Target discovery
Short description of the lab activity	The Laboratory of Translational Hematology and Chemogenomics (THEC) at the University of Parma, led by Professor Giovanni Roti,

	focuses on the identification of novel, pharmacologically actionable molecular targets in aggressive subsets of acute leukemias, both of myeloid and lymphoid origin. The lab employs two primary and complementary research strategies to discover and validate therapeutic vulnerabilities in these diseases. The first is a reverse genetics approach, where the starting point is a known recurrent genetic lesion characterizing a specific molecular leukemia subtype. In this framework, high-throughput chemical and genomic screens are used to identify genes or pathways that are essential for leukemic cell survival in the context of that specific alteration. One of the laboratory's major research lines using this strategy has focused on acute leukemias harboring recurrent mutations involving, for example the MECOM or the NOTCH1 gene, high-risk entities with limited treatment options. Through chemical-genetic interaction mapping, the team has uncovered novel dependencies that could be exploited therapeutically. The second, and highly distinctive feature of this PhD program, is a forward genetics approach—an unbiased strategy aimed at identifying active compounds directly on primary leukemia samples from patients. This is accomplished through a technology called ex vivo drug response profiling (DRP), which enables systematic testing of hundreds of compounds on patient-derived cells to uncover individualized sensitivities, independent of known genomic alterations. This strategy has led to the launch of several national clinical trials designed to match relapsed or refractory leukemia patients with potentially effective drugs, based on functional drug screening rather than solely on genomics. The laboratory has broad genomics expertise, including bulk and single-cell sequencing approaches (e.g., RNA-seq, ATAC-seq), and applies multi-omics integration to characterize disease biology in depth. In addition, the team has strong capabilities in functional proteomics, including mass spectrometry-based phosphoproteomics and chromatin-based RIME (Rapid Immunoprecipitation Mass spectrometry of Endogenous proteins) assays, allowing for comprehensive mapping of signaling and transcriptional networks. Experimental workflows are fully integrated within the laboratory, which houses dedicated space and infrastructure for molecular biology, cell culture, and functional assays. Findings from screening and molecular profiling are validated using patient-derived leukemia xenograft (PDX) models, developed in-house to assess the in vivo efficacy and mechanistic relevance of candidate therapeutic strategies. Overall, the laboratory operates at the intersection of translational research and clinical application, aiming to develop functional precision medicine pipelines that inform the treatment of aggressive leukemias. Through the combination of hypothesis-driven and unbiased methodologies, and by integrating multi-level omic and pharmacologic data, the lab seeks to bridge the gap between genomic discoveries and patient benefit—particularly for high-risk patients who currently lack effective therapeutic options. This environment provides a rich and dynamic training opportunity for PhD candidates, who will be immersed in cutting-edge technologies, interdisciplinary collaborations, and translational science with direct clinical relevance.
Main research area	Genomic Medicine
Group composition	The Translational Hematology and Chemogenomics Laboratory (THEC) was established in 2017 with a startup grant from AIRC, following

	Professor Giovanni Roti's return to Italy after a research tenure at the Dana-Farber Cancer Institute and Harvard Medical School. Since its founding, the laboratory has grown into a dynamic research environment that integrates the work of researchers, postdoctoral fellows, PhD students, and trainees. The current team includes two tenured research scientists (RTD-A), two postdoctoral fellows dedicated to experimental (wet lab) basic research, and two computational biologists supporting data analysis and integration. In addition, the lab hosts two PhD students and typically supervises two to three master's students from the biotechnology or the molecular biology program each year. The laboratory is further supported by two highly skilled laboratory technicians, who play a vital role in both research and in the molecular diagnostics of hematologic malignancies. A major strength of the THEC laboratory is its close integration with the clinical hematology unit at the University of Parma, also led by Professor Roti. This ensures direct access to clinical expertise, facilitates the collection of primary patient samples, and supports the rapid translation of laboratory findings into clinical hypotheses and trials. The synergy between basic and clinical research is a core feature of the lab's mission and workflow. Furthermore, the THEC lab is actively engaged in multiple national and international collaborations, offering PhD students the opportunity to conduct part of their research projects in partnering laboratories abroad. This collaborative network enhances both the scientific scope and the translational impact of ongoing projects, while also providing an enriched training experience in a multidisciplinary, team-based research environment. The successful candidate will also have the opportunity to engage in clinical activities, particularly within the acute leukemia clinical team, in alignment with the focus of the proposed research project. Clinical involvement will be limited to no more than 20% of the candidate's time and may include participation in the care of patients either during inpatient admissions or in outpatient follow-up settings, such as day hospital activities. This clinical exposure is intended to enhance the candidate's understanding of disease context and patient management. However, it will remain limited in scope, as the primary goal of the PhD program is to develop a strong foundation in basic and translational research. The structure of the program is designed to ensure that the candidate gains in-depth experience in laboratory-based science, data interpretation, and integration of molecular and functional analyses, while maintaining a connection to clinical relevance.
Institutional page link	https://www.ao.pr.it/curarsi/reparti-e-servizi-sanitari/ematologia-e-centro-trapianti-midollo-osseo/
Lab website link	https://mc.unipr.it/laboratorio-di-ematologia-traslazionale-e-chemogenomica
Social media link	
Lab bibliography	Identification of an Epi-metabolic dependency on EHMT2/G9a in T-cell acute lymphoblastic leukemia. Montanaro A, Kitara S, Cerretani E, Marchesini M, Rompietti C, Pagliaro L, Gherli A, Su A, Minchillo ML, Caputi M, Fioretzaki R, Lorusso B, Ross L, Alexe G, Masselli E, Marozzi M, Rizzi FMA, La Starza R, Mecucci C, Xiong Y, Jin J, Falco A, Knoechel B, Aversa F, Candini O, Quaini F, Sportoletti P, Stegmaier K, Roti G CELL DEATH DIS 2022 Jun; 13: 551