

Principal Investigator	PASINI DIEGO
Institute of Affiliation	Istituto Europeo di Oncologia I.R.C.C.S. S.r.l.
Title of the proposed project:	Uncovering Therapeutic Vulnerabilities in EZH2-Mutant Germinal Center Lymphomas
Short description of the project	<p>The Polycomb Repressive Complex 2 (PRC2) is a major epigenetic regulator of cellular identity, and its deregulation is a recurrent driver of cancer. Germinal center lymphomas provide a paradigmatic example, as 25-30% of cases harbor heterozygous gain-of-function mutations in EZH2, the catalytic subunit of PRC2. These mutations increase H3K27 trimethylation, resulting in widespread transcriptional repression and altered cell fate programs. Although their oncogenic role has been firmly established, the molecular dependencies that sustain EZH2-mutant lymphoma cells remain poorly defined. The development of tazemetostat (Tazverik), the first FDA-approved EZH2 inhibitor, validated mutant EZH2 as a therapeutic target and demonstrated the clinical potential of epigenetic therapy. However, its recent withdrawal following the emergence of secondary hematologic malignancies highlights the need for alternative therapeutic strategies that selectively target the vulnerabilities created by EZH2 mutations. This PhD project aims to identify the molecular dependencies of EZH2-mutant germinal center lymphomas using advanced functional genomic approaches. Together with the Hematology Division of the European Institute of Oncology (IEO), directed by Prof. Derenzini and in direct collaboration with his research group, the student will establish and apply pooled genetic screening platforms coupled with advanced phenotypic readouts, including high-content imaging, transcriptomic profiling, and single-cell approaches such as Perturb-seq. These complementary strategies will enable the identification of genes and pathways required for the identity and maintenance of EZH2-mutant lymphoma cells. Candidate vulnerabilities will be validated using genomic and epigenomic approaches and assessed on clinically annotated patient samples. The project combines innovative functional genomics with access to patient-derived resources, providing a strong translational framework. By uncovering novel therapeutic vulnerabilities associated with oncogenic EZH2 mutations, it aims to uncover effective treatment strategies, potentially safer, for germinal center lymphomas. The student will receive advanced training in functional genomics, epigenomics, and translational cancer research, complemented by clinical exposure within the IEO Hematology Division.</p>
Main research area for the project	Cancer Biology
5 keywords for the project	Lymphomas - Histone modifications - Drug screening - Epigenetics - Functional genomics

LAB INFO	
Main topic/s of the lab	Epigenetic Mechanisms in Cancer
Short description of the lab activity	Our laboratory investigates the epigenetic mechanisms that regulate cell identity in normal tissues and how their disruption drives cancer development. We combine genetic, biochemical, transcriptomic, and epigenomic approaches with advanced in vivo models and patient-derived 3D organoids to identify disease mechanisms and therapeutic vulnerabilities. By integrating functional genomics with single-cell technologies, our research aims to translate mechanistic insights into novel strategies for precision oncology.
Recent bibliography	<p>BAP1 enhances Polycomb repression by counteracting widespread H2AK119ub1 deposition and chromatin condensation. <i>MOL CELL</i> 2021 Sep; 81: 3526</p> <p>PCGF6 controls murine Tuft cell differentiation via H3K9me2 modification independently of Polycomb repression. <i>DEV CELL</i> 2024 Feb; 59: 368</p> <p>Polycomb group ring finger protein 6 suppresses Myc-induced lymphomagenesis. <i>Life Sci Alliance</i> 2022 Aug; 5:</p> <p>WNT Oncogenic Transcription Requires MYC Suppression of Lysosomal Activity and EPCAM Stabilization in Gastric Tumors. <i>Gastroenterology</i> 2024 Oct; 167: 903</p> <p>Increased genomic instability and reshaping of tissue microenvironment underlie oncogenic properties of Arid1a mutations. <i>Sci Adv</i> 2024 Mar; 10: eadh4435</p>
Group composition	The Pasini's group is currently composed of: 1 Group Scientist 1 Senior Scientist 5 Postdoc of which 3 experimental 1 computational and 1 hybrid with both computational and experimental expertise 6 PhD Students all dedicated to experimental activities 3 post-graduate scientists of which 1 computational 2 Technician of which one senior and one junior
Lab website link	https://www.research.ieo.it/research-and-technology/principal-investigators/diego-pasini/
Social Media Link	https://www.linkedin.com/in/diegopasini/ https://x.com/pasini_lab