European School of Molecular Medicine

2025 summer call PhD selections

AVAILABLE POSITIONS

Principal Investigator	Diego PASINI
Affiliation	European Institute of Oncology, Milan
Title of the proposed project:	Regulatory Mechanisms of Polycomb-mediated Transcriptional Repression in the Control of Cell Identity
Short description of the project	The activities of the Polycomb group (PcG) of repressive chromatin modifiers are essential for maintaining correct transcriptional identity during development and differentiation. Alterations of these activities are common in various human pathologies, making the regulation of Polycomb-mediated repression a highly relevant topic with direct implications for multiple diseases. Cancer and developmental disorders are prime examples, as they often involve driver mutations affecting PcG subunits. PcG proteins are organized into three major repressive complexes - PRC1, PRC2 and PR-DUB - which share overlapping pathways but possess distinct biochemical functions. Understanding the specific roles of these PcG activities is crucial to uncovering the mechanisms by which transcriptional identities are established and maintained. It also provides valuable insight into the oncogenic potential of Polycomb-related mutations and their associated vulnerabilities. This project aims to address key unanswered questions by providing a comprehensive characterization of the mechanisms that regulate the activity of Polycomb Repressive Complexes and their enzymatic products, H3K27me3 and H2AK119ub1. This will involve a multidisciplinary approach to link biochemical insights with in vivo relevance. Using the adult mouse intestine as a model system, we will develop new genetic tools to assess the functional importance of H2Aub1 deposition and its interplay with PRC2 activity and H3K27me3 in transcriptional repression and tissue homeostasis. The project will systematically dissect the contributions of different PRC1 complexes to chromatin landscapes, gene expression programs, and cellular phenotypes during stem cell self-renewal, differentiation, and adult tissue maintenance.
Main research area for the project	Molecular and cellular Biology
Second research area for the project	Cancer biology
3 key words for project	Epigenetics, Polycomb, Cell Identity
Main topic/s of the lab	Epigenetic Mechanisms in Cancer
Short description of the lab activity	Control of cellular identity is regulated by a complex network of autonomous and non-cell autonomous signals that converge to the nucleus and instruct each individual cell to acquire specific transcription programs to exert specific functions. The coordinated activity of DNA binding transcription factors together with a plethora of chromatin modifying and remodelling enzymes is instructed to establish specific transcription programs. These mechanisms are tightly regulated and kept under control to allow

	proper development and or to maintain adult tissue homeostasis. Loss of cellular identity constrains is a common feature of human tumours which frequently involves direct genetic and indirect epigenetic alterations of chromatin remodelling activities more generally defined as epigenetic factors. The central role of these activities, their enzymatic proprieties and the reduced redundancy respect to upstream signalling pathways immediately opens towards the development of novel therapeutic strategies. The work of our laboratory is focused at characterizing the molecular mechanisms underlying distinct chromatin activities under homeostatic and pathological conditions. For this, the lab takes advantage of genetic, biochemical, transcriptomic and epigenomic approaches applied to both *in vivo* and 3D organoids models derived from compound mice or patient samples down to a single cell level. The work in the lab has been recently focused at: • Defining the role of Polycomb repressive activities in adult tissue homeostasis under physiological and pathological conditions. • Dissecting the mechanistic aspects of oncogenic mutations that targets chromatin remodelling activities. Characterizing the epigenetic mechanisms underlying the development of colorectal cancer.
Recent bibliography	1.Tamburri et al. Navigating the complexity of Polycomb repression: Enzymatic cores and regulatory modules. **Mol Cell**, 2024. 2.Mulè et al. WNT Oncogenic Transcription Requires MYC Suppression of Lysosomal Activity and EPCAM Stabilization in Gastric Tumors. **Gastroenterology**, 2024 3.Del Vecchio et al. PCGF6 controls murine Tuft cell differentiation via H3K9me2 modification independently of Polycomb repression. **Dev Cell**, 2024. 4.Conway et al. BAP1 enhances Polycomb repression by counteracting widespread H2AK119ub1 deposition and chromatin condensation. **Mol Cell**, 2021. 5.Tamburri et al. Histone H2AK119 mono-ubiquitination is essential for Polycomb-mediated transcriptional repression. **Mol Cell**, 2020.
Group composition	19 Team Members: 2 Senior Scientists, 5 Postdocs (including 2 Bioinformaticians), 7 PhD Students (including 1 Bioinformatician), 1 Fellow Bioinformatician, 2 Technicians, 2 Undergraduate Students
Institutional page link	https://www.research.ieo.it/research-and-technology/principal-investigators/diego-pasini/
Social media links	linkedin.com/in/diegopasini/ https://x.com/pasini_lab