European School of Molecular Medicine

2026 spring call PhD selections

AVAILABLE POSITIONS

Principal Investigator	PIER GIUSEPPE PELICCI
Institute of Affiliation	European Institute of Oncology

PROJECT INFO	
Title of the proposed project:	Genomic rearrangements at epithelial-gene enhancers as drivers of mesenchymal transition and metastatization in breast cancer: mechanisms of occurrence and transcriptional de-regulation
Short description of the project	Metastases cause over 90% of cancer deaths, yet targeted therapies remain elusive. As they often emerge after surgery, preventing them through neoadjuvant or adjuvant treatments is a promising strategy. However, the lack of therapies directly targeting the metastatization process poses a major challenge, making it crucial to unravel its molecular mechanisms for innovative treatments. Large-scale cancer genome sequencing studies showed that the mutational landscape (single nucleotide variants) of primary and metastatic tumors is largely overlapping, while chromosome instability (CIN) is significantly increased in metastasis (deletions, insertions, inversions, translocations). How mechanistically chromosome instability drives metastatization is unknown. Alternatively, metastatic spreading may be part of adaptive responses to perturbations (phenotype plasticity) originating intra-cellularly (DNA or protein damage), or from the unfavourable tumor microenvironment (nutrient/oxygen deprivation, inflammation). Adaptive responses are orchestrated by master transcription factors (TFs), which induce transcriptional and metabolic reprogramming and the acquisition of new phenotypic states endowing tumor cells with metastatic potential, including motility, immune evasion, ability to survive in circulation and proliferate at distant sites. Examples of metastasis-associated adaptive phenotypes are the Epithelial–Mesenchymal Transition (EMT) in epithelial tumors, and the proliferative-to-invasive switch in melanoma. The interplay between genetic (chromosome instability) and phenotypic (transcriptional reprogramming) traits of metastatization remains unknown. We identified a mechanism linking transcriptional regulation and CIN in epithelial cancers. Specifically, we found that endogenous DNA double- and single-strand breaks accumulate at active enhancers, particularly in regions bound by GRHL2, a master epithelial TF and EMT suppressor. These DNA breaks, enriched in CtIP—a key factor in homologous recombination—are predominantly repaired via error-prone pathways, generating structural variants. Notably, whole-genome sequencing of breast cancer patients reveals frequent chromosomal alterations at GRHL2-bound enhancers, suggesting their role in epithelial identity maintenance. We hypothesize that GRHL2-bound enhancers represent hotspots of DNA damage and genomic rearrangements, disrupting enhancer-promoter interactions and weakening epithelial

	transcriptional programs. This promotes EMT and metastatic dissemination. Our main goals are: i) to analyze the role of CtIP and GRHL2 at target enhancers by integrating their functions in DNA repair and transcriptional regulation in normal epithelial cells; ii) to investigate genomic alterations of GRHL2-bound enhancers in breast cancer, their impact on transcriptional regulation and EMT dynamics, and their potential as prognostic biomarkers. Using genome-wide analyses of DNA damage, chromatin occupancy, 3D genome organization, transcriptomics, and CRISPR-based enhancer perturbation, we will define the contribution of transcription-coupled DNA damage to metastasis. By elucidating the interplay between CIN and transcriptional plasticity, this study may uncover novel vulnerabilities for metastasis-targeting therapies.
Main research area for the project	Cancer Research
Second research area for the project	Cancer Metastasis
3 key words for the project	Enhancers, EMT, Metastases

LAB INFO	
Main topic/s of the lab	Genetic and non-genetic mechanisms of cancer progression and drug resistance
Short description of the lab activity	Since its establishment, my group has focused on identifying critical cancer-associated gene mutations—such as PML-RAR and NPMc+ in leukemia—and corresponding targeted therapies, including the use of retinoic acid to target PML-RAR. We also investigated biological mechanisms underlying tumor maintenance, such as increased symmetric divisions and transcriptional reprogramming in leukemia and breast cancer. Over the past 5–6 years, the focus of our research has shifted significantly toward the characterization of non-genetic mechanisms of tumor progression and maintenance. This transition stems from a key clinical observation: despite the major advances achieved through targeted and immune-based therapies, most patients eventually develop resistance and die from drug-resistant metastatic disease. A growing body of evidence suggests that this failure is often driven by non-genetic mechanisms. Our central aim is to explore whether drug resistance and metastasis result from the ability of cancer cells to dynamically adapt their phenotypes—a phenomenon known as phenotypic plasticity—in response to environmental stressors. These may arise from the tumor microenvironment (e.g., nutrient or oxygen deprivation, inflammation) or from intrinsic cellular stress (e.g., DNA damage, oxidative stress, protein unfolding). Our research strategy involves three main approaches: i) Identification of rare

	subpopulations within primary tumors—pro-metastatic or pro-resistant cells—using transcriptional lineage tracing in human or murine models of breast cancer and AML. ii) Investigation of the mechanisms underlying the mitotic inheritance of adaptive phenotypes, with a focus on candidate chromatin-modifying enzymes. iii) Analysis of how cancer-associated DNA mutations contribute to the emergence of adaptive phenotypes by integrating mutational and transcriptional data at single-cell resolution. Mechanisms identified through these studies are validated in patient samples and assessed for their potential as therapeutic targets. **Current projects include:** i) Characterization of breast cancer phenotypes emerging during metastasis and therapy; ii) Molecular targeting of chemoresistance in AML; iii) Investigation of DNA mutations in the establishment of adaptive phenotypes, including EMT; iv) Study of quiescence-related mechanisms in AML stress adaptation; v) Genotype– phenotype correlation analyses at the single-cell level.
Recent bibliography	Caloric restriction leads to druggable LSD1-dependent cancer stem cells expansion. Nat Commun, 2024 GASOLINE: detecting germline and somatic structural variants from long-reads data Scientific Reports, 2023 High-resolution Nanopore methylome-maps reveal random hyper-methylation at CpG-poor regions as driver of chemoresistance in leukemias Communications Biology, 2023 A Rare Subset of Primary Tumor Cells with Concomitant Hyperactivation of Extracellular Matrix Remodeling and dsRNA-IFN1 Signaling Metastasizes in Breast Cancer Cancer Research, 2023 Inhibition of the lysine demethylase LSD1 modulates the balance between inflammatory and antiviral responses against coronaviruses Science Signaling, 2023 Release of paused RNA polymerase II at specific loci favors DNA double-strand-break formation and promotes cancer translocations. Nat Genet, 2019
Group composition	6 staff scientists, 8 post-doctoral fellows, 4 fellows, 8 PhD students and 3 technicians
Lab website link	https://www.research.ieo.it/research-and-technology/principal-investigators/pier-giuseppe-pelicci/