



RESEARCH ACTIVITY SHEET

2025 PhD selections

YOUR DETAILS

* Name & Surname

Pier Giuseppe Pelicci

* Affiliation IEO

PHD PROJECT DETAILS

* Title of the proposed project

Non-genetic mechanisms of drug-resistance in Acute Myeloid Leukemia (AML)

* Short description of the project (up to 300 words)

AML has a poor prognosis, with a 5-year survival rate below 40%. Standard chemotherapy has remained unchanged for decades, and over 90% of deaths result from chemo-resistant relapse. Emerging evidence suggests resistance is driven by phenotypic plasticity rather than genetic mutations. We developed the first AML PDX models of chemoresistance and, using multi-omic approaches (WES, transcriptional lineage tracing, scRNA-seq), found no specific DNA mutations associated with relapse. Instead, resistant blasts display distinct transcriptional signatures, including IFI6 upregulation. We showed that IFI6 promotes chemoresistance in vivo by antagonizing interferon signaling via cGAS-STING inhibition. This project aims to dissect IFI6's role in resistance through: (1) molecular characterization of IFI6/STING interactions and downstream effects; (2) therapeutic reactivation of interferon signaling using IFN or cGAMP in AML models; and (3) clinical validation of IFI6 as a biomarker via scRNA-seq of patient samples. This work will guide new therapeutic strategies against chemoresistant AML.

The PhD student will receive comprehensive training and gain proficiency in core wet-lab techniques, including mouse genetics, molecular and cellular biology, transcriptional lineage tracing, multi-omic single-cell approaches, high-resolution imaging, and structural biology technologies. Although the computational component of this project is substantial and supported by dedicated personnel, the student will also be expected to become familiar with basic computational biology methods, including single-cell analysis, cancer genomics, clinical data modeling, and multi-omic data integration. The student will join a dedicated team working exclusively on the AML chemoresistance project, which includes one PhD students and one postdoctoral fellow—all fully integrated within the larger host group. While the specific research focus will be defined during the early stages of training, the student is expected to quickly become familiar with the overarching project and to take an active role in shaping her/his individual research direction.

* Indicate the main research area for the project described above Cancer Biology

If needed indicate a second research area for the project described above -

* Provide up to 3 key words for project:

Acute Myeloid Leukemias; multi-omic analyses; in vivo models

YOUR LABORATORY ACTIVITIES DETAILS

* Main topic/s of the lab

Genetic and non-genetic mechanisms of cancer progression and drug-resistance

* Short description of the lab activity (up to 500 words)

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 (max 5 references)

Caloric restriction leads to druggable LSD1-dependent cancer stem cells expansion
Pallavi, R., Gatti, E., Durfort, T., ... Mazzarella, L., Pelicci, P.G.
Nature Communications, 2024, 15(1), 828

GASOLINE: detecting germline and somatic structural variants from long-reads data
Magi, A., Mattei, G., Mingrino, A., ... Mazzarella, L., Pelicci, P.G.
Scientific Reports, 2023, 13(1), 20817

High-resolution Nanopore methylome-maps reveal random hyper-methylation at CpG-poor regions as driver of chemoresistance in leukemias
Magi, A., Mattei, G., Mingrino, A., ... Mazzarella, L., Pelicci, P.G.
Communications Biology, 2023, 6(1), 382

A Rare Subset of Primary Tumor Cells with Concomitant Hyperactivation of Extracellular Matrix Remodeling and dsRNA-IFN1 Signaling Metastasizes in Breast Cancer
Roda, N., Cossa, A., Hillje, R., ... Migliaccio, E., Pelicci, P.G.
Cancer Research, 2023, 83(13), pp. 2155–2170

Inhibition of the lysine demethylase LSD1 modulates the balance between inflammatory and antiviral responses against coronaviruses
Mazzarella, L., Santoro, F., Ravasio, R., ... Minucci, S., Pelicci, P.G.
Science Signaling, 2023, 16(816), ade0326

* Group composition: total members, and roles distribution (PhD, postdoc, technician, etc.)

5 staff scientists, 8 post-doctoral fellows, 1 fellow, 8 PhD students and 3 technicians

Institutional page link

<https://www.research.ieu.it/research-and-technology/principal-investigators/pier-giuseppe-pelicci/>

Lab website link, if any

Social media links, if any

If you prepare a video to promote your lab/project, please include the link below

