PHYSICIAN SCIENTIST
LA MEDICINA INCONTRA LA RICERCA
promosso da: AIRC Fondazione CARIPLO | con il supporto di: SIBMM Società Italiana di Medicina Molecolare, UNIVERSITÀ DEGLI STUDI DI MILANO

| Principal Investigator | Pelicci Pier Giuseppe |
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| **Hosting institution** | Istituto Europeo di Oncologia I.R.C.C.S. S.r.l. |
| **Proposal title** | Dissecting and Targeting IFI6-Driven Chemoresistance in Acute Myeloid Leukemia (AML) |
| **Keywords** | Target therapy; Response and/or resistance to therapy; Chemotherapy and/or chemotherapic drugs; Acute Myeloid Leukemia (AML); DNA methylation |
| **PhD project description** | The project will be carried out at IEO, enabling the candidate to carry out both research (at the experimental oncology department) and clinical activities (in the IEO onco-hematology division). The project stems from an ongoing AIRC grant investigating AML chemoresistance mechanisms. Using patient-derived xenograft (PDX) models recapitulating primary and secondary resistance, we identified a transcriptional interferon (IFN) response signature in chemotherapy-persistent blasts. Silencing of the most upregulated gene of this signature restores chemosensitivity leading to complete leukemia eradication in vivo. Mechanistic studies suggest that the molecular mechanism involves apoptosis induced by STING pathway inhibition. However, pharmacological STING activation only partially restores chemosensitivity, suggesting that STING is either suboptimally activated by the tested compound or additional mechanisms are involved. The project aims at: 1) Biomarker Development - To evaluate the IFN-response signature as predictive biomarkers of chemoresistant relapse in AML. We will perform single-cell RNAseq on peripheral blood or bone marrow samples collected at the end of induction chemotherapy in newly diagnosed AMLs. If a predictive correlation is observed, we will adapt the assay to clinically applicable formats such as bulk RNA-seq or digital-PCR. 2) Preclinical Therapeutic Modeling - To determine whether combining chemotherapy with STING agonists prevents chemoresistant relapse in AML PDXs. We preliminarily tested one STING agonist in combination with chemotherapy, using a 5-day schedule aligned with chemotherapy but at doses established for chronic administration. We will evaluate multiple STING agonists and optimize both dosing and scheduling specifically for concurrent use with chemotherapy. If therapeutic eradication is not achieved, we will test the involvement of additional pathways. To this end, we will reconstruct protein complexes containing the most upregulated gene of the chemotherapy-persistent blast signature, before and after chemotherapy, to identify new actionable effectors. By bridging biomarker discovery with therapeutic modeling, the project is ideally suited for physician-scientist training. |
| **Main topics of the lab** | identification of molecular determinants of therapy resistance in leukemia and breast cancer |

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| **Short description of the lab activity** | The overarching goal of our laboratory is to uncover molecular mechanisms underlying therapy resistance and metastatic dissemination in cancer, with the ultimate aim of developing new tools for patient stratification and treatment. Our research is grounded in the concept that both drug resistance and metastasis can emerge through non-genetic, adaptive mechanisms driven by phenotypic plasticity in response to microenvironmental or intracellular stressors—such as nutrient or oxygen deprivation, immunoediting, inflammation, oxidative stress, or DNA damage. Our work focuses on identifying and characterizing rare pro-metastatic and drug-resistant cell states within tumors, using single-cell and clonal lineage-tracing approaches in robust experimental models of breast cancer (BC) and acute myeloid leukemia (AML). Mechanistic hypotheses are tested in vivo and in vitro using genetic and pharmacological perturbations, and validated in patient samples, with the goal of translating findings into biomarker and therapeutic strategies. In breast cancer, we track the evolution of pro-metastatic clones using lentiviral barcoding and single-cell RNA sequencing. We found that metastases originate from rare clones within the primary tumor that hyperactivate extracellular matrix remodeling and dsRNA/interferon (IFN) signaling. Targeting these pathways reduces metastasis without affecting primary tumor growth. These transcriptional phenotypes predict metastatic progression in patients and are currently being investigated in circulating tumor cells and micrometastases. We are also analyzing the impact of immunoediting on clonal evolution in these models and developing chemotherapy- and immunotherapy-resistant systems to explore how treatments shape the emergence of metastatic clones. In AML, we have developed two PDX models of true chemoresistance and demonstrated that chemotherapy selects for quiescent leukemia-initiating cells (LICs) that survive and later re-enter the cell cycle. These cells activate IFN signaling while downregulating pro-apoptotic dsRNA pathways, suggesting an uncoupling of inflammatory and apoptotic responses. IFI6 emerged as a key regulator of this adaptation. Its inhibition, either genetic or pharmacological, reactivates pro-apoptotic signaling and restores chemosensitivity. We are also testing the effects of LSD1 and DNMT1 inhibitors on the epigenetic states of chemoresistant LICs. Other ongoing projects include: i) investigating the effects of cancer-associated DNA mutations on the establishment of adaptive phenotypes. This is pursued in AML by combined analysis of DNA mutations and transcriptional profiles at single-cell level using SCM-seq, a multi-omic platform that captures gene expression, isoform usage, and mutations across thousands of single cells; and in breast cancer by studying GRHL2-associated enhancer fragility and mutational hotspots in metastasis; ii) dissecting mechanisms involved in the mitotic transmission of adaptive phenotypes, focusing on chromatin architecture (Hi-C, ChIP-seq) and functional roles of chromatin-modifying enzymes, including LSD1 (a histone demethylase) and DNMTs (DNA methyltransferases). Our multidisciplinary approach integrates molecular biology, epigenetics, bioinformatics, translational oncology and leverages cutting-edge technologies provided by the |

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| | departmental technological units (https://www.research.ieo.it/research-and-technology/technological-units/) to dissect adaptive cancer phenotypes and develop actionable strategies to overcome resistance and prevent disease progression. |
| **Main research area** | Cancer biology |
| **Group composition** | The team is constituted by 6 staff scientists, 8 post-doctoral fellows, 8 PhD students and 3 technicians, with broad expertise in a wide range of biological topics, from molecular biology to cell cultures, animal models, and bioinformatics, as well as a deep knowledge in cancer research. |
| **Institutional page link** | https://www.research.ieo.it/ |
| **Lab website link** | https://www.research.ieo.it/research-and-technology/principal-investigators/pier-giuseppe-pelicci/ |
| **Social media link** | nan |
| **Lab bibliography** | 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, Caprioli C, Ronchini C, Frigè G, Semeraro R, Bolognini D, Rambaldi A, Candoni A, Colombo E, Mazzarella L, Pelicci PG Commun Biol 2023 Apr; 6: 382 |