

Principal Investigator BENELLI MATTEO	
Institute of Affiliation	Università degli Studi di Firenze
Title of the proposed project:	Tracking non-tumor-derived cfDNA in longitudinal liquid biopsies to monitor treatment response in metastatic cancer
Short description of the project	<p>This translational and computational PhD project is designed for a physician-scientist seeking to specialize in cancer multi-omics and translational oncology. While liquid biopsy studies in metastatic cancer predominantly focus on tumor-derived alterations, particularly circulating tumor DNA (ctDNA), this project will investigate the non-tumor component of cell-free DNA (cfDNA), including immune-cell and tissue-derived signals, as a dynamic readout of systemic host response during anticancer therapy. The specific research objectives are: - To profile the longitudinal dynamics of non-tumor cfDNA in patients undergoing systemic therapy for metastatic breast and colorectal cancers. - To characterize early therapy-induced modulation of host-derived cfDNA methylation signals, including immune-cell and tissue-of-origin contributions, across serial treatment time points, and assess whether these dynamics are associated with treatment response and early disease progression. The candidate will have access to existing longitudinal plasma datasets profiled by genome-wide DNA-methylation sequencing, integrated with project-specific data generated during the PhD. These molecular profiles are paired with clinically curated information on treatments, outcomes, and, for a subset of patients, matched imaging data. A key clinical component will involve defining clinically meaningful study populations and curating longitudinal clinical datasets, including treatment lines, baseline disease features and key outcomes. The methodological core involves applying state-of-the-art computational methods for signal deconvolution and, where needed, developing AI-based approaches based on informative DNA methylation patterns. These pipelines will refine estimation of cell-type and tissue-of-origin contributions to cfDNA and track their modulation from baseline through early on-treatment time points. A specific clinical placement has not yet been identified; potential host institutions include the Careggi University Hospital and the Azienda USL Toscana Centro, although other options could also be considered.</p>
Main research area for the project	Computational Biology
5 key words for the project	Breast ca., Bioinformatics, Epigenetics, Liquid biopsy, Artificial Intelligence

LAB INFO	
Main topic/s of the lab	Cancer omics, computational oncology, translational research
Short description of the lab activity	The Cancer Omics Laboratory (CAOS lab) conducts research in cancer omics to address fundamental questions in oncology

	<p>concerning cancer origin, evolution, progression and resistance to treatment. The CAOS lab performs integrative analyses of multi-omics data, uses innovative high-throughput omics technologies, and develops new computational approaches and experimental strategies, with a particular emphasis on translational applications (especially liquid biopsy) with the final goal of identifying new prognostic and predictive molecular and/or imaging biomarkers. A summary of current research interests is reported below.</p> <ul style="list-style-type: none"> - Cancer epigenetics and translational applications. Cancer cells exhibit DNA methylation alterations, which lead to dysregulation in gene expression and may impact genome integrity. These epigenetic changes play a crucial role in the initiation and progression of cancer. Our laboratory investigates the significance of these epigenetic alterations, focusing on their utility as biomarkers to inform about molecular phenotypes, to elucidate altered pathways and their application in liquid biopsy techniques. - Integrative analysis of multi-omics cancer data. Cancer is a multifaceted disease originating from alterations of diverse biological mechanisms. Using bioinformatics and machine learning approaches, integrative analysis of multi-omics data enables a comprehensive view of the intricate interactions and dysregulations affecting cancer cells. Our laboratory is involved in AURORA-EU, a large collaborative multi-national project coordinated by Breast International Group (BIG) aimed at improving the understanding of metastatic breast cancer through extensive, multi-omics profiling of paired primary tumors and metastatic biopsy samples. - Computational radiomics. Radiomics refers to the process of extracting and analyzing data from clinical imaging such as CT, MRI, PET and Mammography. The extension of radiomics through its association with molecular omics, referred to as radiogenomics, has shown promising applications, such as informing about relevant genomic alterations, predicting gene expressions patterns and genomic heterogeneity. Our laboratory works on the development of new computational methods for the analysis of radiomics datasets and applies machine learning methods for the development of radiomics-based predictors of patients' outcome and/or cancer phenotypes.
<p>Recent bibliography</p>	<ul style="list-style-type: none"> - Genomic and Transcriptomic Analyses of Breast Cancer Primaries and Matched Metastases in AURORA, the Breast International Group (BIG) Molecular Screening Initiative. <i>CANCER DISCOV</i> 2021 Nov; 11: 2796 - A computational framework for sensitive tumor detection and accurate subtyping using shallow cell-free DNA methylome sequencing. <i>GENOME MED</i> 2026 Feb; 18: - CtDNA detection with low-pass whole genome bisulfite sequencing in RAS wild-type metastatic colorectal cancer: an exploratory objective of the VALENTINO trial. <i>CLIN CANCER RES</i> 2026 Mar; 32: 905

AVAILABLE POSITIONS

	<ul style="list-style-type: none"> - Single-cell transcriptomics reveals biomarker heterogeneity linked to CDK4/6 Inhibitor resistance in breast cancer cell lines. npj Breast Cancer 2025 Jul; 11: 82 - Molecular and Clinical Analyses of Gene Fusions Identify Therapeutic Targets in Paired Primary and Metastatic Breast Cancer from the AURORA Program (BIG 14-01) CLIN CANCER RES 2026 Mar; 32: 947
Group composition	The Cancer Omics (CAOS) lab is composed of 7 members with diverse backgrounds, encompassing both computational and wet-lab expertise. The lab includes 2 postdocs, 2 PhD students, 2 research fellows.
Institutional page link	https://www.sbcs.unifi.it/vp-410-gruppo-benelli.html
Lab website link	https://www.sbcs.unifi.it/vp-410-gruppo-benelli.html
Social media links	https://www.linkedin.com/in/matteo-benelli-220b412b/