PHYSICIAN SCIENTIST
LA MEDICINA INCONTRA LA RICERCA
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Hosting institution	Università degli Studi di Firenze
Proposal title	Investigating the role of peroxisomes in modulating radiotherapy response in breast cancer
Keywords	Breast ca.; Drug response and/or resistance; Estrogens and/or receptors; Response and/or resistance to therapy; Metabolism/Metabolomics
PhD project description	Radiation therapy (RT) remains a cornerstone of breast cancer treatment, especially in early-stage disease and as a postoperative modality. While the molecular mechanisms underpinning resistance to systemic therapies in estrogen receptor-positive (ER+) breast cancer have been extensively investigated, far less is known about cellular processes that contribute to radio-resistance in this subset. Emerging data implicate peroxisomes, key regulators of redox homeostasis, lipid metabolism, and innate immune signaling, as crucial players in therapy adaptation. Given their role in managing oxidative stress, peroxisomes may influence how tumor cells respond to ionizing radiation. This PhD project aims to explore the contribution of peroxisomes to the cellular response and adaptation to RT in ER+ BC. Specifically, the project will: (a) define how peroxisome abundance and activity change upon radiation exposure in ER+ breast cancer models; (b) elucidate how peroxisomes influence redox dynamics, DNA damage response, lipid metabolism and immune signaling; (c) investigate whether modulating peroxisome function (genetically or pharmacologically) alters radiosensitivity and survival post-radiation; (d) identify potential peroxisome-related biomarkers predictive of radio-resistance using patient-derived samples and transcriptomic data. The project will leverage a multidisciplinary approach combining cell line models, 3D organoids, and patient-derived xenografts-organoids (PDXO), complemented by multi-omic profiling (transcriptomics, metabolomics, and redox flux analysis). CRISPR-based perturbation and small-molecule inhibitors will be used to modulate peroxisome function. Radiation response will be assessed through clonogenic survival, DNA damage assays, and immune signaling profiling. This research will uncover novel insights into peroxisome-mediated mechanisms of radio-response and resistance in ER+ breast cancer, potentially revealing therapeutic vulnerabilities and informing precision RT strategies. The findings could pave the way for integrating peroxisome-targeting agents with RT to enhance efficacy and delay recurrence in ER+ breast cancer patients.
Main topics of the lab	Therapy resistance and cancer metabolism
Short description of the lab activity	Our laboratory focuses on understanding the fundamental mechanisms by which metabolic reprogramming supports cancer progression and

	therapy resistance. Metabolic deregulation is not merely a consequence of increased energy demands in proliferating tumor cells, but a driver of tumor initiation, progression, and, importantly, resistance to treatment. A central goal of our research is to dissect how these metabolic alterations contribute to cancer cell survival and adaptation under therapeutic stress, a critical and unresolved challenge in oncology. By leveraging both hypothesis-driven and discovery-based approaches, we investigate the molecular and metabolic underpinnings of resistance to systemic therapies, including endocrine therapy, CDK4/6 inhibitors, and targeted agents, with a specific focus on breast cancers. We aim to define the adaptive mechanisms that allow cancer cells to persist and recur following treatment, and to uncover vulnerabilities that can be therapeutically exploited. To this end, our lab utilizes a wide array of experimental models, including in vitro cell systems, 3D organoids, patient-derived xenografts (PDXs), and mouse models, thanks to an established network of actively renowned collaborators. We integrate multi-omics technologies, such as transcriptomics, metabolomics, and epigenomics, to delineate comprehensive molecular landscapes associated with therapy response and resistance. These analyses are supported by advanced computational pipelines and collaborations with bioinformatic experts. We are actively involved in several research projects: Investigating metabolic reprogramming in endocrine therapy response and resistance in ER+ breast cancer; Exploring metabolic vulnerabilities in triple-negative breast cancer; Studying resistance mechanisms to CDK4/6 inhibitors; Characterizing sex-specific metabolic drivers of NAFLD-to-HCC progression. Our lab is embedded within the Breast Unit of the Azienda Ospedaliero-Universitaria Careggi (AOUC), allowing for close interaction with clinical teams and direct access to patient-derived samples. As the Translational Division of the Breast Unit, we coordinate and lead research activities that aim to bridge basic discoveries with clinical application. A significant and growing line of investigation in our lab focuses on the interaction between systemic endocrine therapy and radiation therapy. In collaboration with clinicians and radiation oncologists, we have designed a prospective clinical trial (HELP) and an associated translational research project aimed at understanding the biological effects of this combinatorial treatment. Through multi-omic profiling of biospecimens collected before and after therapy, we aim to define the molecular changes induced by combined endocrine-radiation therapy, identify biomarkers of response, and uncover mechanisms of resistance. Our research is supported by national and international competitive grants that allow us to pursue high-risk, high-reward projects and to support the training of young scientists in cancer metabolism and translational oncology. Our ultimate goal is to generate actionable knowledge that informs patient stratification, guides therapy decisions, and contributes to the development of more effective and personalized cancer treatments. Clinician applicants admitted to the PhD program will be required to dedicate 20% of their time to clinical duties for the entire duration of the program. These activities will be carried out at the Clinical

	Oncology Unit of AOUC and will be integrated within the operational framework of the Breast Unit.
Main research area	Cancer biology
Group composition	The research group is composed of a multidisciplinary team of 10 core members, including: 2 Staff Scientists with extensive experience in cancer metabolism and therapy resistance, leading key research lines and supporting project development and mentoring. 2 Postdoctoral Fellows, each focused on distinct aspects of metabolic reprogramming in breast and liver cancers. 2 PhD Students currently enrolled in the Biomedical Science program, investigating the role of estrogen signaling and peroxisomes in cancer using advanced multi-omic approaches. 2 Research Fellows, with expertise in experimental and translational tumor biochemistry, actively contributing to multi-omic analyses and patient stratification strategies in breast cancer. 1 Computational Fellow, responsible for the bioinformatic integration and analysis of transcriptomic, epigenomic, and metabolomic data, in collaboration with external computational biology labs. 1 Laboratory Head, who also serves as Head of the Translational Unit of the Breast Unit at the Azienda Ospedaliera Universitaria di Careggi. In addition, the lab plays a key role in training MSc students, hosting approximately 5 students per year, who are fully integrated into ongoing research activities. These students receive hands-on training in experimental techniques, data analysis, and translational project design. The group maintains a strong collaborative link with the Breast Unit, fostering a unique translational environment. Notably, three basic scientists from the Translational Unit are actively involved in lab activities, participate in weekly lab meetings, and regularly share and discuss their research data with the team. This integration ensures continuous dialogue between clinical needs and experimental research, and strengthens the translational relevance of our work. This well-structured and interactive team allows us to pursue high-quality research, mentor young scientists, and accelerate the translation of discoveries into clinical applications.
Institutional page link	https://www.sbsc.unifi.it/
Lab website link	https://www.sbsc.unifi.it/vp-326-gruppo-morandi.html
Social media link	https://bsky.app/profile/andreamorandi.bsky.socialAndrea
Lab bibliography	Integrating radiation therapy with targeted treatments for breast cancer: From bench to bedside. Meattini I, Livi L, Lorito N, Becherini C, Bacci M, Visani L, Fozza A, Belgioia L, Loi M, Mangoni M, Lambertini M, Morandi A CANCER TREAT REV 2022 Jul; 108: 102417