

Principal Investigator	AMBROGIO CHIARA
Institute of Affiliation	Università degli Studi di Torino
Title of the proposed project:	Decoding tumor evolution to optimize sequential RAS-targeted therapies
Short description of the project	<p>The therapeutic landscape of RAS-driven cancers has rapidly evolved with the development of multiple classes of inhibitors, including allele-specific compounds, pan-RAS inhibitors and degraders. While these agents represent a major breakthrough, clinical benefit remains limited by heterogeneous responses and the rapid emergence of resistance. Importantly, there are currently no validated biomarkers to guide the optimal sequencing of these therapies, representing a major unmet need in precision oncology. This project aims to systematically address the complexity of RAS targeting by defining how different classes of RAS inhibitors shape tumor evolution and therapeutic response when used sequentially. We hypothesize that distinct mechanisms of action impose specific selective pressures on tumor cells, leading to predictable patterns of signaling adaptation and resistance that can be leveraged to rationalize treatment sequences. To test this, we will exploit a unique panel of genetically defined KRAS-mutant models developed in our laboratory, enabling direct comparison of multiple RAS-targeted therapies in a longitudinal setting. We will evaluate approved drugs as well as compounds in clinical development, including next-generation inhibitors and degraders, assessing their effects on RAS signaling output and pathway rewiring. Both in vitro systems and in vivo models will be employed to study the dynamic nature of treatment response. Using integrated multi-omics approaches, we will construct a robust "tumor evolution" framework that maps how cancer cells adapt overtime to different therapeutic sequences. This will allow us to identify molecular determinants of sensitivity and resistance and uncover vulnerabilities that emerge during treatment. A key strength of this project is the close integration between basic and clinical research, ensuring that experimental findings are aligned with real-world therapeutic challenges. By providing a mechanistic understanding of how tumors evolve under sequential RAS inhibition, this work has the potential to directly help clinical decision-making and optimize treatment strategies for patients with RAS-driven cancers.</p>
Main research area for the project	Molecular Therapy
5 key words for the project	RAS/RAS inhibitors, Cell signaling, Animal models, Lung ca., Response and/or resistance to therapy

LAB INFO	
Main topic/s of the lab	RAS molecular biology
Short description of the lab activity	The Ambrogio Laboratory (www.ambrogiolab.com ; https://www.ifom.eu/en/cancer-research/researchers/chiara-

	<p>ambrogio.php) investigates RAS oncogenes as central drivers of cancer, with a focus on understanding how aberrant molecular signaling initiates tumorigenesis and shapes response to targeted therapy. RAS-driven tumors represent a major clinical challenge due to the limited durability of current treatments, which are frequently compromised by the rapid emergence of drug resistance. Our research also aims to uncover the early mechanisms of transformation that enable tumor cells to expand and eventually to adapt and survive therapeutic pressure. By integrating advanced in vivo lung cancer models with functional genomics, we dissect how oncogenic signaling networks are rewired during disease progression and treatment. This allows us to identify critical vulnerabilities that can be exploited to improve therapeutic outcomes. Ultimately, we seek to bridge fundamental cancer biology with translational application by defining predictive biomarkers and rational treatment strategies. Our goal is to develop a mechanistic framework that informs how to prevent or overcome resistance, advancing more effective and durable therapies for patients with RAS-driven cancers. The laboratory has a dedicated space comprising fully furnished 100 squared meters of open space laboratory and office desks at the Molecular Biotechnology Center (MBC) within the Department of Molecular Biotechnology and Health Sciences in Torino and a recent new laboratory at IFOM in Milan. The laboratory in MBC is BSL2/BSL3 equipped with instruments for molecular and cellular biology research and has full access to core facilities at the forefront of technological innovation, enabling the realization of the most complex and demanding research projects in basic, translational and pre-clinical areas. In particular, given Dr. Ambrogio's strong background in mouse research, the laboratory offers a modern and fully equipped animal facility with up-to-date imaging instruments including Confocal microscopes, Nuclear Magnetic Resonance, Ultrasound and IVIS Lumina XR imager for bioluminescence experiments in vivo. Facilities for automated high content imaging/screening, mass spectrometry, Next Generation Sequencing (NGS) are available in place. A team of bioinformaticians is available in loco for collaboration on Big Data elaboration.</p>
<p>Recent bibliography</p>	<ul style="list-style-type: none"> - Comparative Analysis and Isoform-Specific Therapeutic Vulnerabilities of KRAS Mutations in Non-Small Cell Lung Cancer. CLIN CANCER RES 2022 Apr; 28: 1640 - Oncogenic mutant KRAS inhibition through oxidation at cysteine 118. MOL ONCOL 2025 Feb; 19: 311 - SOS1 inhibitor BI-3406 shows in vivo antitumor activity akin to genetic ablation and synergizes with a KRASG12D inhibitor in KRAS LUAD. P NATL ACAD SCI USA 2025 Mar; 122: e2422943122 - RAS-ON inhibition overcomes clinical resistance to KRAS G12C-OFF covalent blockade. Nat Commun 2024 Aug; 15: 7554

	<ul style="list-style-type: none"> - EML4-ALK mediates resistance to KRAS G12C inhibition and induces an oncogenic dependency by rewiring signaling through the wild-type RAS pathway. CANCER DISCOV 2026 Jun; :
Group composition	We currently have 16 lab members: 1 PI, 1 Lab Manager, 3 postdocs, 6 PhD students, 2 research fellows, 3 undergrad students.
Institutional page link	https://www.medicinadiprecisione.unicampania.it
Lab website link	https://www.ifom.eu/en/cancer-research/researchers/chiara-ambrogio.php