European School of Molecular Medicine

RESEARCH ACTIVITY SHEET

2025 PhD selections

YOUR DETAILS

* Name & Surname: Alberto Bardelli

* Affiliation IFOM

PHD PROJECT DETAILS

* Title of the proposed project

Modulating DNA Repair Pathways to Enhance Immune Responsiveness in Colorectal Cancer

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

Colorectal cancer (CRC) is one of the leading malignancies worldwide. Although targeted therapies have revolutionized the clinical treatment of cancer patients, chemotherapy remains the standard of care for many CRC patients.
A key challenge in cancer treatment is developing strategies to convert a "cold" (immune-refractory) tumor into a "hot" (immune-responsive) tumor, which remains an unmet clinical need. This project aims to determine whether and to what extent compromising DNA damage repair pathways can disrupt the equilibrium between cancer cells and the immune system, shifting it from tolerance to recognition.
The candidate will employ genetic, pharmacological, and functional screening approaches to gain deeper insights into the potentially actionable immune vulnerabilities of CRC cells.
To address this, the candidate will leverage a CRC biobank containing over 260 two-dimensional cell lines and more than 70 patient-derived organoids, as well as high-throughput technologies and computational methodologies, to identify and characterize how DNA repair alterations can be exploited as a strategy to prevent tumor progression.

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

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

* Provide up to 3 key words for project:

Immune oncology, DNA Repair, colorectal cancer

YOUR LABORATORY ACTIVITIES DETAILS

* Main topic/s of the lab

Our research is focused specifically on precision oncology for CRC, in particular on the characterization of tumor heterogeneity and mechanisms of tumor evolution during therapy administration, with the final aim to identify novel vulnerabilities and therapeutic strategies to prevent or delay the onset of resistance, thus improving survival of cancer patients. In addition, we recently unveiled that cancer cells, alike bacteria in response to antibiotic stress, adaptively down-modulate DNA mismatch repair and homologous recombination proteins, and switch to an error prone-mediated DNA replication process in presence of increased DNA damage when exposed to targeted therapy. Furthermore, immune checkpoint inhibitors have been shown to induce durable responses in a subset of approximately 5% patients with metastatic CRC that carry defective mismatch repair or are microsatellite unstable (MSI). We discovered that inactivation of MMR genes in microsatellite stable (MSS) immune refractory CRCs leads to immune surveillance and response to immune therapy and proposed that this could be pursued for therapeutic purposes. These results led to the ongoing clinical trial ARETHUSA.

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

By using CRC 2D cell lines, 3D patients-derived organoids and xenopatients we defined the mechanisms of primary and secondary resistance to targeted therapies, including how metastatic CRC escape from EGFR, BRAF, TRK, and HER2 inhibition. The use of cancer cell models that replicate the same molecular traits exhibited by tumors of interest in the body, along with the ability to derive them from human samples, enables a detailed study of various aspects of tumor biology, such as the signals driving uncontrolled proliferation. These models also allow for the evaluation of the effectiveness of different anticancer therapies, including immunotherapy. In essence, these models serve as patient-specific "avatars", making it possible to experiment with different treatment approaches to identify the most effective therapeutic options for each individual patient.

In addition to analyzing the genetic profiles of tumors and identifying correlations—referred to as pharmacogenomic associations—between drug activity profiles and the genetic profiles of malignant cells, the laboratory is dedicated to exploring the relationship between the genome and various "omics" disciplines (the study of different molecules derived from genome transcription and their interactions with it), including transcriptomics, methylomics, proteomics, metabolomics, and more. This approach involves an in-depth investigation of the molecular foundations of cancer and resistance to various treatments, with a particular focus on the mechanisms underlying its development.

* Recent bibliography (max 5 references)

Vitiello P.P., et al., and Bardelli A. Cisplatin and temozolomide combinatorial treatment triggers hypermutability and immune surveillance Cancer Cell 2025 [In press]

Mauri G, et al., and Bardelli A. Tumor 'Age' in Early-Onset Colorectal Cancer. Cell 2025 [In press]

Russo M, et al., and Bardelli A. Cancer drug-tolerant persister cells: from biological

questions to clinical opportunities. Nat Rev Cancer. 2024 Oct;24(10):694-717. doi: 10.1038/s41568-024-00737-z, https://www.scopus.com/record/display.uri?eid=2-s2.0-85203011152&origin=resultslist

Amodio V, et al., and Bardelli A. Genetic and pharmacological modulation of DNA mismatch repair heterogeneous tumors promotes immune surveillance. Cancer Cell. 2023 Jan;41(1):196-209. doi: 10.1016/j.ccell.2022.12.003, https://www.scopus.com/record/display.uri?eid=2-s2.0-85145997702&origin=resultslist

Sartore-Bianchi A, et al., and Bardelli A. Circulating tumor DNA to guide rechallenge with panitumumab in metastatic colorectal cancer: the phase 2 CHRONOS trial. Nat Med. 2022 Aug;28(8):1612-1618. doi: 10.1038/s41591-022-01886-0 https://www.scopus.com/record/display.uri?eid=2-s2.0-85135266993&origin=resultslist

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

Main group members at IFOM

Giovanni Germano, Associate Professor
Giovanni Crisafulli, Rosaria Chilà Staff Scientist
Vito Amodio, Paolo Battuello, Veera Ojala, Flaminia Pedretti, Eleonora Piumatti, Nadia Saoudi Gonzalez, Sharon Scardellato, Pietro Paolo Vitiello Postoctoral Fellows
Vittorio Battaglieri, Federico Lazzarini, Giorgio Patelli PhD students
Alessia Anastasia Research Technicians

Main group members at the University of Torino

Mariangela Russo Associate Professor and co-PI
Federica Gentile, Gaia Grasso, Elisa Mariella, Alberto Sogari Postoctoral Fellows
Martina Miotto, Luca Russolillo, Alessia Subrizio PhD students
Simona Lamba, Cristina Ramondetti Research Technicians
Simona Destefanis Administrative Staff

Institutional page link

Lab website link, if any

https://www.ifom.eu/it/ricerca-cancro/ricerca-lab/ricerca-lab-bardelli.php

Social media links, if any

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