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

Principal Investigator	Bardelli Alberto
Hosting institution	Università degli Studi di Torino
Proposal title	Targeting Metastatic Prowess with Translational Oncology
Keywords	Genomics; Chemotherapy and/or chemotherapic drugs; Colorectal and/or Intestinal ca.; Clinical trials; Liquid biopsy
PhD project description	Candidates will join IFOM (The AIRC Institute of Molecular Oncology) and the Bardelli laboratory located in the heart of Milan, an internationally recognized hub for translational oncology. The lab offers long-standing expertise in genomics, translational medicine, computational biology and artificial Intelligence -applied to colorectal and other cancer types. The project will dissect the biological basis of intrinsic tumour aggressiveness through a novel "born to be bad" (BBB) versus "born to be good" (BBG) biological framework. BBB tumours are micrometastatic from the very beginning, persist as minimal residual disease (MRD) after surgery, and spread early. Conversely, BBG tumours remain localized and are cured by surgery alone. No clinical biomarker currently distinguishes these phenotypes, and patients are often treated the same way. This PhD aims to change that. The candidate will work across three integrated platforms: (i) clinical trials applying liquid biopsy to detect MRD in patients and classifying tumours as BBB or BBG; (ii) observational studies collecting human matched tissue, blood, and other samples; (iii) living biobanks of patient-derived organoids, xenografts and cell lines. Multi-omic technologies will span from genome sequencing to novel approaches like digital pathology ("pathomics"). According to candidate preferences, training will cover both wet-lab techniques (e.g., organoid manipulation, in vivo modelling) and/or dry-lab skills (bioinformatics, machine learning, AI-based image analysis) to foster a true physician-scientist profile. Projects can be tailored toward mechanistic experimentation (e.g. modelling BBB traits in vitro/in vivo) or broad vision development, for example building a pan-cancer MRD platform through a large network of clinical collaborations. One day/week of clinical activity at partner hospitals will be arranged in agreement with candidates and clinical directors. The PhD environment is international and multidisciplinary, bringing together physicians, molecular biologists, bioinformaticians, etc. Graduates will emerge with a competitive skill set poised for future academic or industry leadership in precision oncology.
Main topics of the lab	Genomics of Cancer and Targeted Therapies
Short description of the lab activity	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. 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.
Main research area	Genomic Medicine
Group composition	Postdocs: 12 Predoc: 1 PhD Students: 6 Technicians: 4 Staff Scientists: 2
Institutional page link	https://www.mbc.unito.it/it/genomics-cancer-and-targeted-therapies
Lab website link	https://www.mbc.unito.it/it/genomics-cancer-and-targeted-therapies
Social media link	
Lab bibliography	Temozolomide treatment alters mismatch repair and boosts mutational burden in tumor and blood of colorectal cancer patients. Crisafulli G, Sartore-Bianchi A, Lazzari L, Pietrantonio F, Amatu A, Macagno M, Barault L, Cassingena A, Bartolini A, Luraghi P, Mauri G, Battuello P, Personeni N, Zampino MG, Pessei V, Vitiello PP, Tosi F, Idotta L, Morano F, Valtorta E, Bonoldi E, Germano G, Di Nicolantonio F, Marsoni S, Siena S, Bardelli A CANCER DISCOV 2022 Jul; 12: 1656