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

2026 Physician Scientist Call

AVAILABLE POSITIONS

Principal Investigator	**COSTI MARIA PAOLA**
Institute of Affiliation	Università degli Studi di Modena e Reggio Emilia
Title of the proposed project:	Multi-Omics studies of the Mechanism and Toxicity of a Novel Anticancer Drug in Colorectal Cancer
Short description of the project	This research program aims to advance a first-in-class thymidylate synthase (TS) dimer disruptor (DDi) as a novel strategy to exploit nucleotide metabolic vulnerabilities in drug-resistant colorectal cancer (CRC). Unlike conventional TS inhibitors such as 5-fluorouracil (5-FU), which inhibit the catalytic site while stabilizing the active TS homodimer and frequently promote TS accumulation and drug resistance, our allosteric inhibitors (Patent: 102025000013885) destabilize the TS homodimer, inducing rapid proteasomal degradation and sustained TS depletion. This fundamentally distinct mechanism converts nucleotide dependency into replication stress, exposing previously unrecognized therapeutic vulnerabilities. Our lead compounds have demonstrated strong translational potential: Pharmacokinetics: Favorable in vivo pharmacokinetic properties, with a half-life of 10-14 hours following intraperitoneal administration and prolonged exposure after oral dosing. Preclinical efficacy: Robust antitumor activity in colorectal cancer xenografts, ovarian cancer xenografts, and orthotopic pancreatic ductal adenocarcinoma (PDAC) mouse models, demonstrating efficacy comparable or superior to 5-FU across multiple tumor settings. Mechanistic activity: TS dimer destabilization induces rapid TS degradation, nucleotide imbalance, replication stress, DNA damage, ATR-CHK1 checkpoint activation, G2/M arrest, and apoptotic cell death, identifying TS as a critical metabolic vulnerability. Cancer stem cell targeting: DDis efficiently eradicate colorectal cancer spheroid cells (CR-CSphCs), maintaining activity independently of basal TS expression and targeting clinically relevant models of tumor heterogeneity and therapeutic resistance. The proposed research will integrate state-of-the-art non-animal methodologies (NAMs) with a comprehensive systems biology approach, combining quantitative proteomics, metabolomics, transcriptomics, advanced bioinformatics, and Oxford Nanopore DNA sequencing performed at the Human Technopole National Facility for Genomics. This allows to reach specific objectives related to understanding the mechanism of action at a deeper level, bioinformatic analyses will identify patterns of genomic instability, structural DNA alterations, and DNA damage-associated signatures linked to nucleotide depletion and replication stress. Then a verification process to integrate the different results will be performed.
Main research area for the project	Molecular Therapy
5 key words for the project	Pharmacology, Proteomics, Drug response and/or resistance, Drug discovery and/or development, DNA damage

LAB INFO	
Main topic/s of the lab	Drug discovery and development. Mass Spectrometry Proteomics and metabolomics studies on samples from cancer cells models and patients, in collaboration with clinical scientists
Short description of the lab activity	Our laboratory specializes in anticancer drug discovery, integrating mass spectrometry-based proteomics, metabolomics, and bioinformatics to characterize novel therapeutics. Working within an interdisciplinary network, we combine medicinal chemistry, molecular oncology, to accelerate lead identification, mechanistic validation, and preclinical development. Our pipeline extends from target discovery to translational advancement toward Phase I clinical trials. In close synergy with biotechnology and pathology experts, we investigate drug-target engagement, signaling pathways, and the DNA damage response. Our primary objective is to translate innovative compounds into clinical applications, establishing markers of therapeutic response and overcoming resistance in high-risk cancers. Advanced Multi-Omics: The Clinical scientist will work on this subject. Using high-resolution mass spectrometry, he/she will perform comprehensive proteomic, metabolomic and bioinformatic profiling to map mechanism and toxicity cellular responses; he/she will identify signaling pathway modulation and assess drug-induced metabolic reprogramming. These analyses are integrated with molecular and cellular biology approaches to elucidate biological mechanisms and identify predictive biomarkers. This represents the core activity of the scientist enrolled in the research program. Cancer Cell Models: Advanced cancer cell models used to screen and characterize the innovative therapeutic candidates, provides insights into efficacy, mechanisms of resistance, and potential toxicities. Main pathways involved are replication stress, DNA damage response, and biomarker discovery enables functional validation of novel anticancer agents. Clinical Partnership: A cornerstone is the close collaboration with clinical scientists from IRST IRCCS "Dino Amadori" (Meldola) and the MITO (Multicenter Italian Trials in Ovarian Cancer and Gynecologic Malignancies) Group. By integrating data from preclinical models and patient-derived samples, we bridge the gap between bench and bedside, ensuring that candidate compounds are optimized for clinical translation. This multidisciplinary network supports biomarker discovery and validation of therapeutic strategies in colorectal and other solid tumors, strengthening the translational impact of our research. Operative plan: Clinical samples already available and newly ones from the mentioned collaboration, will be selected based on statistical design to achieve significant results. Samples from CRC drug resistant patients will be prepared following internal laboratory protocols and subjected to MS analysis at the CIGS center. Data analysis will be ensured using Mascot and then Proteome discover for protein identification and analysis. Then bioinformatic studies will be performed using STRING and other similar software. Different statistical methods will be adopted including Machine learning methods. Cell-based studies will be conducted to compare the agreement/disagreement with the cellular condition. The subsequent step: all data (from all existing experiments) will be stored in a common platform to ensure intraoperability of data for use in different software, (FAIRDOMSEEK) and then appropriate software will be adopted to characterize the mechanism, efficacy and safety of the new candidate. Collaboration will be established for this virtual analysis study. The final outcome will be first level entry predictive efficacy and safety profile of the candidate. This will allow to plan next step experiments avoiding unnecessary workload and animal testing. The clinical

	scientist can perform the clinical duties in the Policlinico Hospital (UNIMORE) or Santa Maria (Reggio Emilia)
Recent bibliography	- Folic Acid-Peptide Conjugates Combine Selective Cancer Cell Internalization with Thymidylate Synthase Dimer Interface Targeting. J MED CHEM 2021 Mar; 64: 3204 - Destabilizers of the thymidylate synthase homodimer accelerate its proteasomal degradation and inhibit cancer growth. eLife 2022 Dec; 11: - Serum Mass Spectrometry Proteomics and Protein Set Identification in Response to FOLFOX-4 in Drug-Resistant Ovarian Carcinoma. CANCERS 2023 Jan; 15: - Enhanced anticancer effect of thymidylate synthase dimer disrupters by promoting intracellular accumulation. FRONT PHARMACOL 2024; 15: 1477318 - A stretch-responsive fibroblast program promotes epidermal stem cell self-renewal during skin expansion. NAT COMMUN 2026 Jun; :
Group composition	Unimore Drug discovery & biotechnology & molecular oncology. The Research laboratory consists of a network of different laboratories: 1. Drug discovery and biotechnology (PI prof. MPCosti) - omics studies and bioinformatics; 2. molecular biology and pharmacology Prof. D Darca and G.Marverti; 3. center of large instruments (CIGS) equipped with Mass Spectrometry instruments of different types, imaging instruments (https://www.cigs.unimore.it) - this si connected with lab 1. 4. Clinical scientist laboratory, anatomy pathology Prof. Lorena Losi. 5. Oxford Nanopore DNA sequencing performed at the Human Technopole National Facility for Genomics. 6. IRST IRCCS "Dino Amadori" (Meldola) for clinical samples We have currently 2 PhD students, 2 postdoc for pharmacology research (animal trials of the drug candidate are ongoing), 1 postdoc in molecular modeling for drug target interaction studies. 6 thesis students.
Institutional page link	https://unimore.unifind.cineca.it/get/person/014268
Lab website link	https://www.mariapaolacosti.com
Social media links	https://www.linkedin.com/feed/update/urn:li:activity:7477018055806676992/