PHYSICIAN SCIENTIST
LA MEDICINA INCONTRA LA RICERCA
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Principal Investigator	Polo Simona
Hosting institution	IFOM - Istituto Fondazione di Oncologia Molecolare, ETS
Proposal title	Decoding Early Metastasis in Colorectal Cancer: The Hidden Role of Alternative Splicing
Keywords	Wnt/beta-catenin pathway; Cell signaling; Colorectal and/or Intestinal ca.; Metastasis; RNA splicing
PhD project description	Despite progress in screening, diagnosis, and treatment, colorectal cancer (CRC) remains the second leading cause of cancer-related mortality worldwide. Originating from stem cells in the colonic crypt, CRC arises through genetic and epigenetic changes that lead to neoplastic transformation. Mutations in tumor suppressors (e.g., APC, TP53, SMAD4) and oncogenes (e.g., KRAS) drive its progression. The most lethal phase involves tumor invasion and spread. Although metastasis accounts for most CRC deaths, no consistent metastasis-specific driver mutations have been identified, leaving its molecular basis unclear and limiting targeted therapeutic development. The traditional model of stepwise progression has been challenged by the identification of "born to be bad" (BBB) CRCs, which exhibit early dissemination of metastasis-competent cells, as opposed to "born to be good" (BBG) tumors that are micrometastatis-negative as defined by the absence of circulating cell-free tumor DNA. Recognizing CRCs with early metastatic potential is crucial for risk stratification and therapeutic intervention. Our laboratory has uncovered a novel cancer-intrinsic mechanism contributing to early metastasis: alternative splicing (AS) reprogramming driven by nuclear β-catenin. AS generates multiple protein isoforms from a single gene. We have found that activated β-catenin suppresses a key splicing factor, promoting cancer-specific isoforms associated with invasion and metastasis across multiple CRC subtypes. We hypothesize that AS acts as a regulatory layer enhancing tumor adaptability and plasticity in early metastatic CRCs. Using CRC organoids and unbiased RNA sequencing, we are profiling AS signatures that distinguish BBB from BBG tumors. Our goal is to link specific alternatively spliced isoforms to early metastatic behavior, thereby identifying novel biomarkers and therapeutic targets. This project will equip a physician-scientist with critical expertise in molecular and cancer biology, transcriptomics and reverse genetic engineering approaches. The candidate will join a multidisciplinary, collaborative and friendly lab where continuous training is pursued at all levels.
Main topics of the lab	Ubiquitin signaling pathways and alternative splicing programs in physiology and cancer
Short description of the lab activity	The Laboratory of Molecular Machines in Signaling Pathways investigates molecular mechanisms underlying signaling pathways commonly deregulated in cancer. Since its foundation, the lab directed

	by Prof. Simona Polo, has established a strong legacy in ubiquitin biology, elucidating how this small, versatile post-translational modifier regulates protein fate and function through diverse chain topologies and linkage types. Our work has been instrumental in defining ubiquitin's roles beyond proteasomal degradation, particularly in endocytosis, signal transduction, and subcellular organization. We have also characterized key features of E3 ubiquitin ligases, which confer substrate specificity and dictate the functional outcome of ubiquitin conjugation. More recently, the lab has expanded its focus to alternative splicing, a fundamental mechanism that enhances proteomic diversity and functional complexity. This shift reflects a refinement of our research framework: we propose that a deeper understanding of tumor biology requires moving beyond the genomic characterization of oncogenes toward the study of proteoforms generated through post-transcriptional and post-translational regulation. These regulatory layers are central to cellular plasticity, enabling cancer cells to dynamically adapt and evolve resistance to therapy. A unifying theme across our research is the capacity of both ubiquitin signaling and alternative splicing to remodel protein structure and function. Each mechanism introduces variation at the protein level, altering interaction networks, subcellular localization, and activity. Critically, both are co-opted in cancer to drive malignant transformation, immune evasion, and therapeutic resistance. By investigating these processes mechanistically, we aim to uncover how they converge to rewire signaling networks in disease. To address these complex questions, the laboratory employs a multidisciplinary approach. We utilize patient-derived organoids and advanced 3D cellular models to investigate the functional relevance of splicing alterations in a context that closely mimics human disease. Cell-free biochemical systems enable the reconstitution of ubiquitination cascades, allowing precise dissection of enzymatic mechanisms. Functional genomics, including CRISPR-based screens, is used to systematically interrogate the roles of splicing factors and ubiquitin-related genes. Leveraging IFOM's advanced facilities, we use proteomics to analyze protein isoforms and ubiquitin modifications, and next-generation sequencing to profile splicing landscapes and their regulatory architecture. Furthermore, high-resolution microscopy and structural biology techniques are applied to study E3 ligases and protein complexes at the molecular level, providing insights into the dynamic interactions that govern specificity and function. The integration of these methodologies not only deepens our understanding of cellular regulation but also supports the identification of novel therapeutic strategies, leveraging mechanistic knowledge to uncover vulnerabilities in cancer.
Main research area	Cancer biology
Group composition	2 staff scientist, 2 postdocs, 4 phD students, 2 master students
Institutional page link	https://www.ifom.eu/en/cancer-research/programs/molecular-machines-signalling-pathways.php
Lab website link	
Social media link	
Lab bibliography	Hecw controls oogenesis and neuronal homeostasis by promoting the liquid state of ribonucleoprotein particles. Fajner V, Giavazzi F, Sala S, Oldani A, Martini E, Napoletano F, Parazzoli D, Cesare G, Cerbino R, Maspero E, Vaccari T, Polo SNAT COMMUN 2021 Sep; 12: 5488