PHYSICIAN SCIENTIST
LA MEDICINA INCONTRA LA RICERCA
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Principal Investigator	Damia Giovanna
Hosting institution	Istituto di Ricerche Farmacologiche "Mario Negri" I.R.C.C.S.
Proposal title	Overcoming poly-ADP-rybose-polymerase inhibitor resistance in ovarian carcinoma
Keywords	Pharmacology; DNA repair; Response and/or resistance to therapy; Ovarian ca.; Poly-ADP-ribose polymerase (PARP)
PhD project description	Poly(ADP-ribose) polymerase inhibitors (PARPis) have transformed the treatment options available for ovarian carcinoma, improving progression-free survival, particularly in patients with defects in homologous recombination repair. However, resistance to therapy eventually emerges and poses an obstacle to cure. Using different preclinical models, the project aims to: - dissect the molecular and cellular factors of olaparib resistance in vivo using complementary approaches; Identify biomarkers of response to olaparib, including validating the RAD51 foci score in a cohort of ovarian cancer patients; assess new combination strategies to delay and/or overcome olaparib resistance. State-of-the-art omics technologies will be employed to profile the genome and assess the expression of mRNA and miRNAs during the acquisition of olaparib resistance in the PDX preclinical models available in our laboratory. Studies of the tumour microenvironment in the olaparib-resistant syngeneic mouse model may reveal modifications that occur with the acquisition of resistance. The RAD51 foci score will be prospectively validated in a cohort of ovarian cancer patients enrolled in the Iolanthe study: a phase IIIb-IV trial aimed at confirming the efficacy of olaparib in combination with bevacizumab as a frontline maintenance treatment for HRD-positive ovarian tumours. Omics studies on the available PDXs and data generated in acquired olaparib-resistant models will reveal pathways involved in drug resistance, which will be validated and targeted in order to overcome or revert drug resistance, and which may lead to the identification of new predictive biomarkers of response. The development of novel and effective combinations of olaparib with other drugs to overcome/delay olaparib resistance will be prioritized for clinical evaluation. This project is highly relevant from a medical perspective, as it focuses on PARPi resistance. With the introduction of these agents at an early stage in the treatment of ovarian cancer patients, this will represent an important medical need in the near future.
Main topics of the lab	Sensitivity and resistance to therapy in ovarian cancer
Short description of the lab activity	The Preclinical Gynaecological Oncology laboratory is part of the Experimental Oncology department at the Istituto di Ricerche Farmacologiche Mario Negri IRCCS in Milan. The laboratory has all the necessary equipment, expertise and preclinical models to carry out experiments investigating the mechanisms of sensitivity and resistance

	to both cytotoxic agents (including platinum drugs such as cisplatin) and targeted agents (including poly-ADP ribose inhibitors such as olaparib, and DNA damage targeting agents such as CHK1, WEE1, ATR and ATM inhibitors) in ovarian cancer. Specifically, the laboratory's activities include: -in vitro activities: cytotoxic activities; high-throughput technologies for screening drug libraries; CRISPR-Cas9 technologies; drug-induced cell cycle perturbation; apoptosis/ferroptosis detection; fiber assay (to study the dynamics of the replication fork); different DNA repair tests; -molecular studies: RNAseq; RT-PCR, western blot, immunohistochemistry, immunofluorescence techniques and screening of lentivirus CRISPR-Cas9 libraries; -vivo experiments (patient-derived xenograft models of ovarian carcinoma and syngeneic mouse models of ovarian carcinoma that are sensitive or resistant to platinum drugs and poly(ADP-ribose) polymerase inhibitors). The laboratory has the dedicated instruments required to perform all these techniques, including nucleic acid extractors, thermocyclers, western blot apparatuses, real-time PCRs, spectrophotometers, a histology laboratory, a confocal microscope, a sterile room for cell cultures, incubators, a cell counter, microscopes and a cytofluorimeter. In addition, the laboratory has access to the Institute's Animal Facility with dedicated spaces and instruments (IVIS). The laboratory collaborates closely with the Computational Oncology Unit in the Department of Oncology at the Istituto di Ricerche Farmacologiche Mario Negri IRCCS, which supervises the processing of all omics data and works closely with all members of the laboratory to interpret the data. In recent years, the laboratory's focus has been on mechanisms of resistance to anticancer agents and DNA repair as possible mechanisms of resistance/sensitivity to anticancer agents. The laboratory has also focused on preclinical in vitro and in vivo models to test the activity of anticancer agents and signalling transduction pathways involved in the DNA damage checkpoint (Chk1, p53, ATM, BRCA and FA), as well as gene expression profiles, mainly in ovarian carcinoma. We have a xenobank containing more than 60 models of patient-derived ovarian carcinomas, whose molecular, histological and pharmacological characterization has enabled studies on the role of biomarkers of response to therapy (e.g. RAD51 and BRCA1 foci) in formalin-fixed paraffin-embedded tumour samples. These models also represent a useful tool for testing new, effective therapies for this tumour type. Over the past few years, we have derived different cisplatin- and olaparib-resistant models in vivo from sensitive ones, which will be instrumental for the development of the present project. The availability of these models has enabled the study of tumour metabolism in response to therapy through ad hoc in vivo experiments using the Seahorse instrument, in close collaboration with the Mass Spectrometry Laboratory at the Istituto di Ricerche Farmacologiche Mario Negri.
Main research area	Molecular Therapy
Group composition	Total members: 8 members 2 senior staff members 1 post-doc 3 PhD students 1 Master student
Institutional page link	https://www.marionegri.it/
Lab website link	

Social media link	
Lab bibliography	VEGF pathway inhibition potentiates PARP inhibitor efficacy in ovarian cancer independent of BRCA status. Bizzaro F, Fuso Nerini I, Taylor MA, Anastasia A, Russo M, Damia G, Guffanti F, Guana F, Ostano P, Minoli L, Hattersley MM, Arnold S, Ramos-Montoya A, Williamson SC, Galbiati A, Urosevic J, Leo E, Cavallaro U, Ghilardi C, Barry ST, Bani MR, Giavazzi R J HEMATOL ONCOL 2021 Nov; 14: 186