PHYSICIAN SCIENTIST
LA MEDICINA INCONTRA LA RICERCA
promosso da: AIRC Fondazione CARIPLO | con il supporto di: SEMM European School of Molecular Medicine | UNIVERSITÀ DEGLI STUDI DI MILANO

2026 Physician Scientist Call

AVAILABLE POSITIONS

Principal Investigator	**TONON GIOVANNI**
Institute of Affiliation	Università Vita-Salute San Raffaele
Title of the proposed project:	Targeting mitochondria to prevent cancer tolerance and persistency
Short description of the project	Minutes after exposure to antibiotics, bacteria mount an intense response, named tolerance, to withstand even exceedingly high doses of antibiotics. In the clinic, tolerance is responsible for antibiotic treatment failures and bacterial infection relapses. We recently demonstrated that tolerance is present also in cancer cells, interfering with cancer treatment (Punzi et al., Nature Communications). As in bacteria, this tolerant response evolves towards persistence, whereby only a subpopulation survives treatment. As for the mechanism driving the transition from tolerance to persistency, we identified a defining feature of persister cells, that is, a prominent increase in mitophagy, the process where mitochondria are degraded and recycled. Importantly, blocking mitophagy erased tolerant cells. Of note, patients presenting an activated mitophagy signature present a markedly poor survival. Therefore, interfering with mitophagy is a promising avenue to tackle one of the most pressing clinical needs, eliminate dormant, residual cancer cells. In this project, we will leverage a microfluidic platform that we have devised, that allow the screening of hundreds of patient-derived organoids (PDOs), miniature, 3D multicellular tissue cultures grown in the lab from a patient's own biological samples. In the last decade, the use of PDOs has become a central tool for therapeutic screening and precision medicine, since PDOs closely mimic the heterogeneity at single cell level of a tumour tissue and match patient response to therapy. We will focus on metastatic colon cancer to the liver, one of the most intractable cancers. We will generate and validate reporter systems, where GFP will be placed under the control of the promoter of genes activated during mitophagy. We will then screen drug libraries, seeking to identify compounds able to quench mitophagy. The most promising candidates will be then validated into orthotopic mouse models, where PDOs will be injected in the mouse liver.
Main research area for the project	Molecular Therapy
5 keywords for the project	Drug response and/or resistance - Chromatin remodeling – Autophagy – Metastasis - Organ-on-chip

LAB INFO	
Main topic/s of the lab	The Functional Genomics of Cancer laboratory seeks to discover the fundamental mechanisms of carcinogenesis and to identify effective cures to treat cancer.

Short description of the lab activity	In this project the PhD student will be trained in basic molecular and cellular biology techniques. With the support and help of senior members of the lab and of the PI, the student will learn the strategy to design a reporter system, to generate it, and to insert it into cancer cell lines and patient-derived organoids. The student will become acquainted with generating and growing PDOs, high-throughput screenings into the microfluidic device, and how to read and interpret the ensuing data. Finally, the student will be trained in handling mice and perform in vivo experiments. Lab members benefit of a fully equipped and dedicated laboratory space and cell culture facility, state-of-the-art Flow Cytometry/Sorting facility, Specific Pathogen Free Animal Facility, including a Mouse Clinic within the burgeoning reality of the San Raffaele Scientific Institute. Moreover, critically important for the success of this proposal, is the scientific environment: the San Raffaele Institute is one of the leading research Centres in Italy, a world-renowned institution that has attracted brilliant scientists from disciplines as diverse as neuroscience, gene therapy, clinical sciences, genetics and cancer. State-of-the- art facilities, alongside the impressive critical mass of cutting-edge scientific know-how, collaborative environment and expertise make this Centre an ideal place for pursuing creative and high-impact science.
Recent bibliography	Early tolerance and late persistence as alternative drug responses in cancer. NAT COMMUN 2025 Feb; 16: 1291 Harnessing oncology real-world data with AI. Nature Cancer 2023 Dec; 4: 1627 Evolutionary fingerprints of epithelial-to-mesenchymal transition. NATURE 2025 Apr; 640: 1083 Chromatin Velocity reveals epigenetic dynamics by single-cell profiling of heterochromatin and euchromatin. Nat Biotechnol 2022 Feb; 40: 235 Spatial epitranscriptomics: from Cinderella to queen. NAT METHODS 2026 Jun;
Group composition	The lab provides an excellent environment to learn and thrive, with several PhD students, at various degrees of training, post-doctoral fellows and some senior scientists overseeing activities. The lab has a strong connection with genomic and bioinformatic expertise. The projects in the lab are quite diverse, all focusing on cancer. They range from high-throughput genetic and drug screenings to uncover new cancer liabilities and the causes of resistance to therapy, several projects on cancer plasticity and epigenetics, seeking to identify the mechanisms by which chromatin remodelers disrupted in cancer are oncogenic and how epigenetics is exploited by cancer cells to thrive and resist therapy.
Institutional page link	https://research.hsr.it/en/index.html
Lab website link	https://research.hsr.it/en/divisions/experimental-oncology/functional-genomics-of-cancer/giovanni-tonon.html