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TEMPLATE RICHIESTA ATTIVAZIONE TOPIC AGGIUNTIVI SU FONDI PNRR

D.M. 9 aprile 2022 n. 351

Project title/Titolo del Progetto	**Unraveling the complexity of cellular interactions using patient-derived 3D cancer models**
Principal Investigator	Roncalli Massimo/ Terracciano Luigi
Main field of interest/Ambito principale di ricerca	3D cancer modeling, network interaction analysis
Abstract	Tumors comprise both neoplastic cells and a diversity of non-neoplastic host components, defined as the tumor microenvironment (TME) which promotes carcinogenesis, tumor progression, and metastases of malignant cells. The complex TME includes mesenchymal-derived cells, resident or infiltrating vascular structure, and the immune cellular network1 . Bidirectional communication between cells and their microenvironment is critical for both normal tissue homeostasis and tumor growth. In particular, interactions between tumor cells and the associated TME represent a powerful relationship that influences disease initiation, progression, and response to therapy2 . Organotypic cultures, such as 2D cell lines, usually contain only one cell type representing the neoplastic epithelium and lack the multicellular representation of the TME. On the other hand, in vivo xenografts and genetically engineered animal models are either costly and/or do not sufficiently recapitulate the complex genetics and TME interactions of human tumors. Furthermore, preclinical development of drugs such as immunotherapies (e.g. immune checkpoint inhibitors) and TME agents have predominantly relied upon murine models in which the degree of stress severity is 2 or 3. The implementation of TME-containing patient-derived 3D models will help reduce or replace animal experimentation. Our proposal seeks to establish 3D in vitro models that adequately recapitulate the tumor architecture and mimic the cell-to-cell interactions within the TME. The development of these models will provide the means 1) to study how cells communicate under different stimuli and 2) to rationally design clinical trials to reduce failure rates. The specific aims of this project are 1) to generate disease specific 3D models that maintain the tumor tissue architecture and mimic the pathophysiological microenvironment using freshly resected human specimens, 2) to evaluate the potential of TME-containing 3D models for ex vivo drug screening

	and 3) to define and characterize the cellular interactions among the cell populations in the generated models and matched tumors.
Type of Co-funding	○ D.M. 351/2022 - Borse di dottorato per la transizione digitale
Lab name and address	Pathology
Brief description of the coherence of the Project in relation to the PNRR objectives[3]	The present project will create ex vivo interaction modeling that mimics complex cellular interaction allowing High-throughput drug screening thus favoring the development of innovative therapeutic approach to perform precision medicine. The project will be developed in institution with great expertise in liver pathology, tumor modeling and bioinformatics and is coherent and consistent with the Ph. D. program. Data and new pipeline developed will be published on public repository as Zenodo and GitHub respectively. Open access publication will be preferred as possible. The project will meet the aim of the PNRR in particular will fill the gap of technical skills in the research.
N. of months abroad (min. 6, max. 18) [**compulsory**]	10
Name of the research institution/company abroad	University of Basel, Department of Biomedicine, Visceral Surgery and Precision Medicine laboratory (PI: Piscuoglio)
N. of months of internship (min. 6, max. 18) [compulsory only for D.M. 352/2022]	0
Name of the company[3]	NA
Scientific references	1. Dijkstra, K.K. et al. (2018) Generation of tumor-reactive T cells by co-culture of peripheral blood lymphocytes and tumor organoids. Cell 174:1586–1598. 2. Sato, T. et al. (2011) Long-term expansion of epithelial organoids from human colon, adenoma, adenocarcinoma, and Barrett's epithelium. Gastroenterology 141:1762-72. 3. Seino, T. et al., (2018) Human Pancreatic Tumor Organoids Reveal Loss of Stem Cell Niche Factor Dependence during Disease Progression. Cell Stem Cell 22(3):454-467.e6. 4. Jenkins, R.W. et al., (2018) Ex Vivo Profiling of PD-1 Blockade Using Organotypic Tumor Spheroids. Cancer Discov. 8:196-215. 5. Neal, J.T. et al., (2018), Organoid Modeling of the Tumor Immune Microenvironment. Cell 175:1972–1988.
Type of contract	PhD scholarship of € 18.000 gross per year awarded by Humanitas University. This sum is exempt from IRPEF income tax according to the provisions of art. 4 of Law no. 476 of 13th August 1984, and is

	subject to social security contributions according to the provisions of art. 2, section 26 and subsequent sections, of Law no. 335 of 8th August 1995 and subsequent modifications.