UNIVERSITÀ DEGLI STUDI DI MILANO-BICOCCA
DOTTORATO DI RICERCA IN Tecnologie Convergenti per i Sistemi Biomolecolari – XLII CICLO

Research Topic ID: XLII – 1.14

Project Tutor: Prof. Renata Tisi

Project Supervisor/s: Prof. Elena Sacco

Project Title: Exploring advanced cellular models and tools of spatial analysis to identify novel metabolic vulnerabilities in cancer research

Scientific background & Objectives
Metabolic reprogramming is one of the hallmarks of cancer [1,2], playing an important role in tumorigenesis, metastasis, and drug resistance [3,4]. It represents an opportunity to identify new diagnostic/prognostic markers and clinical targets. Metabolic rearrangements in the tumor are influenced by interactions between cancer cells and the tumor microenvironment. To face tumor complexity, it is necessary to use advanced preclinical models that are as representative as possible of the three-dimensional architecture, nutritional gradient, and cellular composition of the tumor mass [8,9].

The objectives of the project are:
- develop reliable and reproducible 3D cancer models of solid tumors from tumor cell lines including increasing grades of complexity
- study the morpho-functional alterations occurring in these cellular models through a top-down unbiased approach based on omics analyses
- study the physiological and metabolic alterations, possibly with spatial resolution, with different technologies including Seahorse, and high content analysis by confocal and multi-photon microscopy.
- validate data by spatial omics analyses and quantitative imaging on cancer tissue specimens.

Project's Networks, Sustainability & Mobility

a) The hosting lab competences/tools
- Our laboratory has been involved in different projects aiming to identify novel targets of cancer, and in recent years, it has acquired expertise in developing three-dimensional cancer models for this purpose, such as spheroids and organoids from patients with bladder cancer and from patient-derived xenografts of breast cancer. The methodologies that our laboratory has applied to the study of cancer metabolism include Seahorse technology, confocal microscopy, and flow cytometry. Moreover, our laboratory has received funding for the PNRR project Elixir, which allowed the purchase of a multi-photon microscope for advanced imaging analysis.

b) Intradepartmental or external collaborations
- Prof. Daniela Elena Costea (Bergen, Norway), Dr. Chiara Raggi (University of Florence) – can share expertise on co-cultures of CAFs and cancer cells.
- SYSBIO (Dr. Daniela Gaglio), Prof. Fulvio Magni and Dr. Andrew Smith (Unimib)– can collaborate for metabolomics analysis.

UNIVERSITÀ
DEGLI STUDI DI MILANO-BICOCCA

DIPARTIMENTO DI
BIOTECNOLOGIE E BIOSCIENZE

BtBs
Dipartimento di Biotecnologie e Bioscienze

TeCSBi PhD

- Prof. Fabio Pagni and Dr. Davide Seminati (Pathology Unit, Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy) can provide bladder cancer tissue specimens for retrospective studies
- Prof. Rocco Piazza (Unimib), Prof. Daniela Besozzi (Unimib), Prof. Chiara Damiani (Unimib) Prof. Renata Tisi – can collaborate to perform spatial transcriptomic analysis and data integration.

c) Pertinent research article published by the proposer
- Pasquale et al. 2020 [10], Damiani et. al 2020 [11], Campioni et. al 2022 [12], Di Filippo et.al 2022 [13], Proietto et al. 2023 [14],

d) Putative foreign institutions for achieving the required ordinary mobility (6 months)
(A) Gade Laboratory for Pathology, Department of Clinical Medicine and Centre for Cancer Biomarkers CCBio, Haukeland University Hospital, University of Bergen, N-5021 Bergen (Norway), Prof. Daniela Elena Costea.
(B) Sbarro Institute of Cancer Research and Molecular Medicine and Center for Biotechnology, Temple University, Philadelphia (PA, USA), Prof. Andrea Morrione / Prof. Antonio Giordano.

References
[1] Hanahan, D.; Weinberg, R.A. Hallmarks of cancer: the next generation Cell 2011 *144*(5), 646–674.
[2] Hanahan D. Hallmarks of Cancer: New Dimensions. Cancer Discov. 2022 Jan;12(1):31-46.
[3] Park, J.H.; Pyun, W.Y.; Park, H.W. Cancer Metabolism: Phenotype, Signaling and Therapeutic Targets. Cells 2020, *9*(10), 2308.
[4] Peiris-Pagès, M.; Martinez-Outschoorn, U.E.; Pestell, R.G.; Sotgia, F.; Lisanti, M.P. Cancer stem cell metabolism. Breast Cancer Res. 2016 18(1):55.
[5] Boedtkjer, E.; Pedersen, S.F. The Acidic Tumor Microenvironment as a Driver of Cancer. *Annual Review of Physiology*. 2020, 82, 103–126.
[6] Lyssiotis, C.A.; Kimmelman, A.C. Metabolic Interactions in the Tumor Microenvironment. *Trends in Cell Biology*. , 27(11) , 863–875. 2017
[7] Trédan, O.; Galmarini, C.M.; Patel, K.; Tannock, I.F. Drug resistance and the solid tumor microenvironment. *Journal of the National Cancer Institute*. , 99(19) , 1441–1454. 2007
[8] Zanoni, M.; Cortesi, M.; Zamagni, A.; Arienti, C.; Pignatta, S.; Tesei, A. ,J. Hematol. Oncol. *13*(1), 1–15
[9] Langhans, S.A. ,Front. Pharmacol. *9*(JAN), 1–14
[10] Pasquale, V.; Ducci, G.; Campioni, G.; Ventrici, A.; Assalini, C.; Busti, S.; Vanoni, M.; Vago, R.; Sacco, E., Cells (2020), 9(12), 1–26
[11] Damiani, C.; Gaglio, D.; Sacco, E.; Alberghina, L.; Vanoni, M. Systems metabolomics: from metabolomic snapshots to design principles. Current Opinion in Biotechnology. 2020 63, 190–199.
[12] Campioni, G.; Pasquale, V.; Busti, S.; Ducci, G.; Sacco, E.; Vanoni, M., Cells 2022 11(5), 866
[13] Filippo, M. Di; Pescini, D.; Galuzzi, B.G.; Bonanomi, M.; Gaglio, D.; Mangano, E.; Consolandi, C.; Alberghina, L.; Vanoni, M.; Damiani, C. INTEGRATE: Model-based multi-omics data integration to characterize multi-level metabolic regulation. 2022; 1–31 pp.
[14] Proietto, M.; Crippa, M.; Damiani, C.; Pasquale, V.; Sacco, E.; Vanoni, M.; Gilardi, M., Front. Oncol. 2023 13:1164535.