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

Research Topic ID: XLII – 1.4

Project Tutor: Chiara Damiani

Project Supervisor/s: Federica Facciotti

Project Title: Gut Microbiota and Tumor Metabolism in Colorectal Cancer

Scientific background & Objectives

Colorectal cancer (CRC) displays a profound metabolic reprogramming1 to support tumor growth, immune evasion and therapy resistance[1]. In parallel, the gut microbiota has emerged as a key modulator of the colonic metabolic environment, through the production, consumption and transformation of bioactive metabolites[2]. While numerous studies have reported associations between microbiota composition, metabolite abundance and host transcriptional programs[3,4], the functional relationship between microbial activity and tumor nutrient consumption remains poorly understood.
Current approaches often study tumor metabolism indirectly through gene expression analysis, without explicitly addressing nutrient uptake and metabolic fluxes, while microbiome studies typically focus on metabolite levels or taxonomic profiles.
The aim of this project is to investigate the functional relationship between gut microbiota features and tumor nutrient consumption patterns in CRC to identify metabolic interactions that may inform therapeutic or preventive strategies.
The student will leverage existing transcriptomic and microbiome datasets together with advanced metabolic modeling[5,6] and machine-learning approaches.

Project's Networks, Sustainability & Mobility

a) the coherence of the suggested project with competences/tools of the hosting lab
b) intradepartmental or external collaborations
c) at least one pertinent research article published by the proposer/s
d) 1 (or more) putative foreign institutions for achieving the required ordinary mobility (6 months)

a) The project fully aligns with Chiara Damiani's lab's extensive experience in constraint-based metabolic modeling applied to cancer, including the development of approaches to infer nutrient uptake and secretion profiles from transcriptomic data, as well as spatially resolved analyses of tumor metabolic heterogeneity.

b) The project will benefit from existing external collaborations with CNAG (Barcelona, Spain), which can provide paired host–microbiota spatial transcriptomics datasets. CNAG may also be considered for external co-tutoring. Intradepartmental collaborations will be activated with Federica Facciotti, an expert in the intestinal microenvironment. Existing internal collaborations with Marco Vanoni's lab, with expertise in cancer metabolism and advanced cellular models, will also be maintained. Moreover, the lab is establishing collaborations with Francesca Cordero's lab at the University of Turin, which has expertise in computational microbiota modeling.

c) Pertinent research articles published by the proposer:

- Maspero, Davide, et al. “Spatial FBA reveals heterogeneous Warburg niches in renal tumors and lactate consumption in colorectal cancer”. *npj Systems Biology and Applications*, 2026.
- Lin, Lihao, et al. "Mechanistically informed machine learning links non-canonical TCA cycle activity to Warburg metabolism and hallmarks of malignancy." *PLOS Computational Biology* 21.12 (2025): e1013384.
- Damiani, Chiara, et al. "Integration of single-cell RNA-seq data into population models to characterize cancer metabolism." *PLoS computational biology* 15.2 (2019): e1006733.
- Damiani, Chiara, et al. "A metabolic core model elucidates how enhanced utilization of glucose and glutamine, with enhanced glutamine-dependent lactate production, promotes cancer cell growth: The WarburQ effect." *PLoS computational biology* 13.9 (2017): e1005758.
- Di Filippo, Marzia, et al. "INTEGRATE: Model-based multi-omics data integration to characterize multi-level metabolic regulation." *PLoS computational biology* 18.2 (2022): e1009337.

d) Putative foreign institutions for mobility include European or international research centers active in cancer systems biology, metabolic modeling or microbiome research, such as:

- Anna Pascual’ lab at Centro Nacional de Análisis Genómico (CNAG), Barcelona, Spain
- Vassily Hatzimanikatis’s lab at École Polytechnique Fédérale de Lausanne (EPFL), Switzerland
- Claudio Angione’s lab at Teesside University

References

[1] Pang, Boran, and Hao Wu. "Metabolic reprogramming in colorectal cancer: a review of aerobic glycolysis and its therapeutic implications for targeted treatment strategies." *Cell Death Discovery* 11.1 (2025): 321.
[2] Krautkramer, Kimberly A., et al. "Diet-microbiota interactions mediate global epigenetic programming in multiple host tissues." *Molecular cell* 64.5 (2016): 982-992.
[3] Wirbel, Jakob, et al. "Meta-analysis of fecal metagenomes reveals global microbial signatures that are specific for colorectal cancer." *Nature medicine* 25.4 (2019): 679-689.
[4] Visconti, Alessia, et al. "Interplay between the human gut microbiome and host metabolism." *Nature communications* 10.1 (2019): 4505.
[5] Mardinoglu A, Nielsen J. Systems medicine and metabolic modelling. *Journal of Internal Medicine*, 2012.
[6] Maspero, D., et al. "Spatial flux balance analysis reveals region-specific cancer metabolic rewiring and metastatic mimicking." *npj Systems Biology and Applications*, 2026.