BiomeHEAT: A Microbiome-Modulating therapy to reactivate Cytotoxicity in ICI not-responding CRC patients

Paola Pinco[1], Federica Perillo[1,2], Alberto Baeri[1], Paola Maragno[3], Bruna Caridi[1], Francesco Strati[1], Federica Facciotti[1,2]
E-mail: paola.pinco@unimib.it
[1] Department of Biotechnology and Biosciences, University of Milano-Bicocca, Milan, Italy
[2] Department of Experimental Oncology, European Institute of Oncology IRCCS, Milan, Italy
[3] Gastroenterology and Endoscopy Unit, Fondazione IRCCS Cà Granda, Ospedale Maggiore Policlinico, Milan, Italy

Keywords: Colorectal cancer; Microbiome; Cytotoxic T cells; Immunotherapy.

Abstract:
The pivotal role played by the immune system in the antitumoral responses has been widely recognised and is still matter of study. However, the capability of malignant cells to evade immune recognition can compromise immune system cytotoxic activity against tumour.
The administration of monoclonal antibodies targeting checkpoint inhibition (ICI) is a good strategy to reactivate the immune system against malignant cells, primarily in dMMR/MSI-H metastatic colorectal cancer (CRC) patients. Nevertheless, a proportion of them manifest primary or secondary resistance to ICI.
Since the gut microbiota is a key player in controlling mucosal immune tolerance, its modulation is becoming increasingly important in the oncology field to enhance responsiveness to therapies. In particular, microbiome modulating therapies (MMTs) may improve the efficacy of immunotherapy and reduce correlated adverse events. For instance, minimal microbial ecologies (MMEs) can enhance responsiveness to immunotherapies in CRC patients, by restoring their immune cells' cytotoxic functions.

Thus, the first aim of this study is to formulate synthetic MMEs stimulating T cell cytotoxic functions and subsequently to validate them in preclinical models (in vitro, ex-vivo, in vivo). Then, we want to evaluate the safety of the strongest MMEs candidates' administration in healthy volunteers. To maximise the success, a broad number of synthetic ecologies will be generated with different approaches and will be tested in vitro, so that the most promising MMEs candidates will proceed to in vivo preclinical models testing and, finally, the strongest candidate(s) will be evaluated in a phase 1 trial with healthy volunteers.

This project allows to move quickly from bench to bedside by providing practical tools in the form of rationally designed synthetic microbial ecologies, potentially effective in treating CRC patients.