

<b>PI</b>	<i>Maria Rescigno</i>
<b>PROJECT TITLE</b>	The microbiota in tumor metastases formation
<b>ABSTRACT</b>	<p>We found that the microbiota may have beneficial effects on tumor progression (Zagato et al., 2020). However, it may also be involved in the formation of tumor metastases. We described in the intestine the existence of a vascular barrier (Gut Vascular Barrier, GVB) that resembles the blood brain barrier (BBB) (Mouries et al., 2019; Spadoni et al., 2017; Spadoni et al., 2015). This barrier controls the entrance of molecules and the microbiota through the portal circulation to the liver and systemic sites. We hypothesized that the GVB might control the translocation of neoplastic cells from the primary tumor into the portal circulation in colorectal cancer (CRC).</p> <p>We carried out a retrospective analysis on resected human CRC and healthy controls. We found a higher expression of a marker for GVB disruption (PV-1) in the tumors of patients with distant metastases in the follow up and with reduced progression-free survival, indicating that PV-1 is a marker of poor prognosis.</p> <p>We found that GVB impairment is required for : 1. The migration of bacteria from the primary tumor to the liver; 2. the formation of a premetastatic niche which recruits inflammatory cells and in turn tumor cells; 3. the formation of metastases in the liver (Bertocchi et al., 2021). In this project, we want to characterize the premetastatic niche and the bacteria population in the liver.</p>
<b>FUNDING REFERENCE (AMOUNT, STARTING DATE AND DURATION)</b>	AIRC 5x1000 Immunity in Cancer Spreading and Metastasis ISM – 1.800.000 euro 2018-2024
<b>MAIN TECHNICAL APPROACHES TO CARRY OUT THE PRESENT PROJECT</b>	<p>Microbiome and microbiota analysis</p> <p>Bacteria isolation and functional testing</p> <p>Tumor models</p> <p>Immune cell phenotyping</p> <p>Molecular and cellular biology</p>
<b>SCIENTIFIC REFERENCES RELATED TO THE PRESENT PROJECT</b>	<p>Bertocchi, A., Carloni, S., Ravenda, P.S., Bertalot, G., Spadoni, I., Lo Cascio, A., Gandini, S., Lizier, M., Braga, D., Asnicar, F., <i>et al.</i> (2021). Gut vascular barrier impairment leads to intestinal bacteria dissemination and colorectal cancer metastasis to liver. <i>Cancer Cell</i>.</p> <p>Mouries, J., Brescia, P., Silvestri, A., Spadoni, I., Sorribas, M., Wiest, R., Mileti, E., Galbiati, M., Invernizzi, P., Adorini, L., <i>et al.</i> (2019). Microbiota-driven gut vascular barrier disruption is a prerequisite for non-alcoholic steatohepatitis development. <i>J Hepatol</i>.</p> <p>Spadoni, I., Fornasa, G., and Rescigno, M. (2017). Organ-specific protection mediated by cooperation between vascular and epithelial barriers. <i>Nat Rev Immunol</i>.</p> <p>Spadoni, I., Zagato, E., Bertocchi, A., Paolinelli, R., Hot, E., Di Sabatino, A., Caprioli, F., Bottiglieri, L., Oldani, A., Viale, G., <i>et al.</i> (2015). A gut-</p>

vascular barrier controls the systemic dissemination of bacteria. *Science* 350, 830-834.

Zagato, E., Pozzi, C., Bertocchi, A., Schioppa, T., Saccheri, F., Guglietta, S., Fosso, B., Melocchi, L., Nizzoli, G., Troisi, J., *et al.* (2020). Endogenous murine microbiota member *Faecalibaculum rodentium* and its human homologue protect from intestinal tumour growth. *Nat Microbiol* 5, 511-524.