PROJECT 1

DoS: Prof. Marco E Bianchi

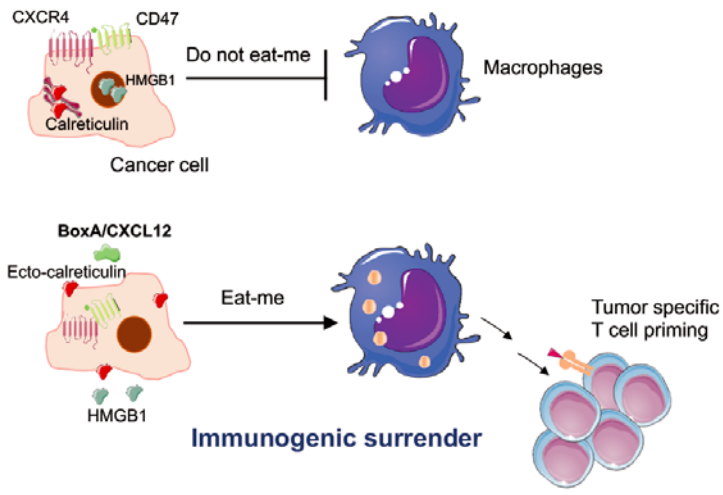
Title: CXCR4-mediated antitumor immunization

Curriculum: BAIO

Link to OSR/UniSR personal page: https://www.unisr.it/docenti/b/bianchi-marco-emilio

Project description (*Number of characters, including spaces*: 2.000 - 3.000):

This PhD position, funded by an AIRC project started in 2021, is to investigate the molecular and cellular mechanisms of a novel of immunosurvellaince process that we named ImmunoGenic Surrender (IGS). Recent work in our lab (1) has unveiled an antitumor activity of CXCR4, a G-Protein Coupled Receptor. Tissue regeneration and cancer progression often recapitulate developmental processes, involving the same pathways and key players. The alarmin HMGB1 and the chemokine CXCL12 promote the regeneration of multiple tissues via the activation of CXCR4 (2,3). CXCR4 activation also promotes cancer growth and invasion (1,3).
Unexpectedly, we found that CXCR4 activation flags tumor cells to immune recognition (1). Both CXCL12, a natural CXCR4 ligand, and BoxA, a fragment of HMGB1, promote the exposure of Damage Associated Molecular Patterns and the internalization of CD47, a "don't eat me" signal. Treatment with BoxA leads to phagocytosis of tumor cells by macrophages, and protective T-cell-dependent antitumor immunity in mice. We called this process ImmunoGenic Surrender because tumor cells turn themselves in to the immune system, thereby subjecting a rapidly growing (but "illegal") tissue to immunological scrutiny.
The project consists in understanding whether CXCL12, which generally promotes tumor growth, does in fact promote tumor rejection as well via IGS. We expect a dual result: some mice will succumb earlier because of the tumor growth effect, and some mice will reject the tumor due to the orthogonal IGS effect. Increased tumor rejection will be evidence that IGS depends on CXCL12. This will only be a proof-of-principle, with low translational value because of the inherent risks of accelerating tumor development in at least some individuals. However, the student will investigate the cellular signal transduction pathway of CXCL12 binding to tumor cells, and how to exploit it to promote IGS without promoting cell proliferation. Finally, we want to understand which cells mediate IGS in vivo, focusing on macrophages (either tumor-resident or monocyte-derived) and DCs.
Although this is primarily a project of basic immunology and cell biology, there is a potential translational application to cancer therapy.



Skills to be acquired by the student (*Number of characters, including spaces*: max 600):

- work with cancer models developed in-house, including mice, organoid and 3D in vitro models

- learn about immune responses to cancer and how to measure them using multiple assays, primarily flow cytometry and cell imaging

References (max. 15)

1. Mezzapelle R, ... and Bianchi ME (2021) CXCR4 engagement triggers CD47 internalization and antitumor immunization in a mouse model of mesothelioma. EMBO Mol Med 13: e12344.doi: 10.15252/emmm.202012344
2. Tirone M, ... Bianchi ME* and V✓©n✓©reau E* (*equal contribution). High Mobility Group Box 1 orchestrates tissue regeneration via CXCR4. J Exp Med 2018, 215: 303-18. doi: 10.1084/jem.20160217
3. Bianchi ME and Mezzapelle R (2020) The chemokine receptor CXCR4 in cell proliferation and tissue regeneration. Front Immunol 11:2109. doi: 10.3389/fimmu.2020.02109.