PROJECT 1

DoS: Emilie VENEREAU

Title: Exploring HMGB1-directed strategies to fight cancer

Curriculum: BAIO

Link to OSR/UniSR personal page: https://research.hsr.it/en/divisions/genetics-and-cell-biology/units/tissue-regeneration-and-homeostasis.html

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

Cancer is a leading cause of mortality worldwide accounting for millions of deaths each year. Systemic inflammation remains an important area for novel therapeutic targets in combating both tumor progression and cachexia, a very debilitating muscle wasting syndrome affecting most of cancer patients. High Mobility Group Box 1 (HMGB1), the main trigger of sterile inflammation, appears as a promising therapeutic target in cancer. This nuclear protein is released to act as a signal of tissue damage and HMGB1 dysfunction is associated with each hallmark of cancer. The aim of the PhD project is to pave the way for innovative HMGB1-directed therapeutic strategies for patients with cancer.

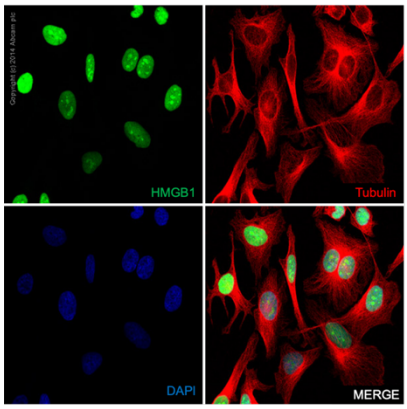

Figure: HMGB1 expression in tumor cells. Representative images of HMGB1 (green signal), alpha-tubulin (red signal) and DAPI staining (blue signal) in HeLa cervical cancer cells. Picture adapted from Abcam website.

We previously demonstrated that the multiple activities of HMGB1 depend on its redox state, which is determined by the microenvironment (1, 2). We generated a non-oxidizable mutant of HMGB1 devoid of proinflammatory properties but with potent regenerative molecule in multiple tissues (3). Preliminary data indicate that this designer molecule counteracts tumor progression in different mouse models of carcinogenesis.
The objectives of the current project are: 1) to determine whether the different redox isoforms of HMGB1 play diverse roles in tumor growth and cancer cachexia, 2) to evaluate the therapeutic properties of the non-oxidizable mutant of HMGB1 in mouse models of cancer. To address these key questions, we will combine the use of novel tools generated in our laboratory (recombinant HMGB1 redox isoforms, conditional HMGB1 KO mice) with well-established mouse models of cancer cachexia that will be investigated with the most up to date molecular, cellular and imaging procedures. The project is funded by AIRC.
In summary, the aim of this PhD project is to provide the answer to a long-lasting question: is HMGB1 good or bad for tumor? We suspect that the answer will be: it depends on its redox state.

Skills to be acquired by the student:

Technical skills: cell culture, molecular biology, flow cytometry, histology, mouse models of cancer, novel transgenic mice; IT skills: Microsoft Office, GraphPad Prism software, online resources and tools (NCBI), FACS Analysis software, ImageJ, Photoshop, Illustrator software; Communication skills: oral presentations (lab meetings, internal seminars, oral presentations at national and international conferences), article writing (research articles and reviews).

References (max. 3)

1- Venereau E, et al. Mutually exclusive redox forms of HMGB1 promote cell recruitment or proinflammatory cytokine release. J Exp Med (2012).

2- Ferrara M, et al. Oxidation of HMGB1 Is a Dynamically Regulated Process in Physiological and Pathological Conditions. Front Immunol (2020).

3- Tirone M, et al. High Mobility Group Box 1 orchestrates tissue regeneration via CXCR4. J Exp Med (2018).