PROJECT 2 (optional)

DoS: Marta Muzio

Title: Dissecting and targeting NFAT signaling in chronic lymphocytic leukemia

Curriculum: BAIO

Link to OSR/UniSR personal page:
https://research.hsr.it/en/divisions/experimental-oncology/cell-signaling.html

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

Chronic lymphocytic leukemia (CLL) is characterized by the accumulation of clonal mature B-cells in the peripheral blood and lymphoid organs; CLL cells are strongly dependent on B-cell receptor signaling molecules as witnessed by the recent approval of drugs targeting different BCR-associated kinases. Nonetheless, BCR stimulation leads to the activation of distinct transcription factors including NFAT whose constitutive activation has been reported in chronic lymphocytic leukemia (CLL) as well as other B-cell malignancies (1). Targeting NFAT in CLL has been recently proposed as a novel potential therapeutic approach based on preclinical data using a specific peptide that blocks NFATs activation and translocation into the nucleus; the addition of the VIVIT peptide *in vitro* induced apoptosis of leukemic cells, and reduced tumor growth *in vivo* in mouse models (2). The aim of this PhD project is to functionally dissect the signaling framework of different NFAT family members, and to optimize NFAT pharmacological targeting in CLL.

To achieve this, we will:

Perform ChIP-seq, and gene editing followed by RNAseq analyses to identify and characterize the target genes of different NFAT family members in normal and leukemic cells. These studies will drive the characterization of novel potential biomarkers of NFAT activation/inhibition.

Test different nanconstructs targeting NFATs activation by using preclinical models of CLL including primary cells, cell lines and mouse models (2,3).

Skills to be acquired by the student:

Cellular and molecular biology techniques including genomics and transcriptomics (gene editing, ChIP-seq and RNA-seq).

Independent critical thinking; experimental planning and design; data analysis and data/progress reports; seminar presentations to the scientific community.

References (max. 3)

1) *Role of NFAT in chronic lymphocytic leukemia and other B-cell malignancies.* Sana I, Mantione ME, Angelillo P, Muzio M. Front. Oncol., 01 April 2021, https://doi.org/10.3389/fonc.2021.651057

2) *Targeting B-cell anergy in chronic lymphocytic leukemia.* Apollonio B, Scielzo C, Bertilaccio MT, Ten Hacken E, Scarfò L, Ranghetti P, Stevenson F, Packham G, Ghia P, Muzio M*, Caligaris-Cappio F*. Blood. 2013 May 9;121(19):3879-88

3) *Interleukin-1 receptor-associated kinase 4 inhibitor interrupts toll-like receptor signalling and sensitizes chronic lymphocytic leukaemia cells to apoptosis.* Delvecchio VS, Sana I, Mantione ME, Vilia MG, Ranghetti P, Rovida A, Angelillo P, Scarfò L, Ghia P, Muzio M. Br J Haematol. 2020 May;189(3):475-488.