PROJECT 1

DoS: Renato Ostuni

Title: Dissecting genomic regulatory interplays in tumor-associated macrophages

Curriculum: Basic and Applied Immunology and Oncology (Cell Gene Therapy Program)

Link to OSR/UniSR personal page:
http://www.hsr.it/research/organization/institutes/sr-tiget/renato-ostuni/

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

Macrophages are specialized innate immune cells with central roles in homeostasis and disease. Upon exposure to micro-environmental stimuli, these cells can adopt a variety of phenotypes ranging from immune stimulation and cytotoxicity to immune suppression and tissue repair. Dynamic transitions between these functional properties in response to tumor signals are thought to underlie the generally pathogenic role of macrophages in cancer. At the same time, macrophage plasticity could be exploited to therapeutically reprogram the phenotype of tumor-associated macrophages (TAMs) cells by pharmacological, cell and gene therapy approaches.

In this project, the successful candidate will investigate how anti-inflammatory stimuli that are frequently upregulated in cancer impact on the capacity of macrophages to mount efficient inflammatory responses. To this aim, ex vivo cultures of primary bone marrow-derived macrophages and freshly isolated TAMs will be used to dissect the transcriptional and epigenomic programs instigated by tumor-promoting signals and to identify potential targets for therapeutic reprogramming. State-of-the-art genome engineering technologies will be exploited to validate and define the mode of action of putative candidates, followed by in vivo validation in relevant tumor models.

We aim to elucidate how macrophages integrate incoherent environmental stimuli at the genomic level, and translate them into context-specific gene expression programs. Because concomitant activation of antagonistic pro-inflammatory and anti-inflammatory pathways is almost invariably observed in cancer, we propose that these interplays are critical determinants of the biology of tumor-associated macrophages. Our approach integrates cutting-edge genomics and computational modelling with in vitro functional screenings and in vivo manipulation of macrophages, building on uniquely available gene therapy platforms. Successful completion of this project will generate widely exportable paradigms of gene regulation in the immune system, and deliver innovative cell and gene therapy strategies to manipulate the behaviour of macrophages in cancer.

Skills to be acquired by the student:
The student will gain a unique combination of expertise in: state-of-the-art technologies for epigenomic and transcriptome analysis at the single cell-level; mouse tumor models; gene engineering of hematopoiesis; bioinformatics tools and analyses

References (max. 3)

1. Piccolo V, ... and Ostuni R*, Natoli G*. Opposing macrophage polarization programs show extensive epigenomic and transcriptional cross-talk. Nat Immunol. 2017 Mar 13. doi: 10.1038/ni.3710.

2. Ostuni R, Kratochvill F, Murray PJ, Natoli G*. Macrophages and cancer: from mechanisms to therapeutic implications. Trends Immunol. 2015 Apr;36(4):229-39.

3. Ostuni R et al. Latent enhancers activated by stimulation in differentiated cells. Cell. 2013 Jan 17;152(1-2):157-71.