PROJECT 1

DoS: Paolo Dellabona

Title: Adoptive immunotherapy of hepatic colorectal cancer metastasis with functionally engineered innate-like T cells

Curriculum: Basic and Applied Immunology and Oncology

Link to OSR/UniSR personal page: http://research.hsr.it/en/divisions/immunology- transplantation-and-infectious-diseases/experimental-immunology.html

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

Liver metastases from colorectal cancer, the second most common cause of cancer death worldwide, are a major unmet clinical need, because current treatments, including the newest immunotherapies by immune checkpoint blockade, are effective only in a minority of patients. Hence, there is pressing need for more efficacious therapeutic approaches. Adoptive cell therapy (ACT) with tumor-specific T cells has proven successful in controlling, at least temporarily, disseminated metastatic tumors also of epithelial origin. However, to achieve long-term control, ACT requires to be further enhanced by counteracting the different immunosuppressive mechanisms that characterize the tumor microenvironment. This is particularly relevant for hepatic metastasis, in which the natural tolerogenic milieu already active in the liver at the steady state may synergize with the cancer-induced immunosuppression. In light of these considerations, main aim of this project is to devise at the pre-clinical level an ACT strategy that leverages a peculiar group of T cells, called innate-like T cells, which account for up to 50% of total hepatic T lymphocytes in mice and man. In particular, the project will harness the functions of CD1d-restricted invariant Natural Killer T (iNKT) and of MR1-restricted Mucosal Associated Invariant (MAIT) cells. We have recently shown that iNKT cells have potent anti-tumor functions, exerted via modulation of myelomonocytic cells in the tumor microenvironment (1,2). It is unclear whether also MAIT cells share a similar activity. iNKT and MAIT cells will be functionally enhanced by engineering with tumor-specific TCRs and/or a selected group of anti-tumor cytokines (IL-15, IL-12, IL-7, IFN□), and assessed in ACT experiments in mice bearing hepatic metastases of colorectal cancer. In parallel, immunomodulatory molecular and cellular pathways activated in the liver by metastatic cancers, in the presence or absence of iNKT or MAIT cells, will be deciphered using state-of-the art single cell analysis entailing RNA sequencing, high content tissue multiplexing and high dimensional flow cytometry. The combination of the information obtained in the project should inform the design of optimized ACT for deadly CRC liver dissemination.

Skills to be acquired by the student: this project is part of a Program recently funded by AIRC to the Institute entitled*: "*Advanced immune gene and cell therapies for liver metastases", involving 17 amongst research and clinical groups working at OSR. The student working on this project will acquire hands-on expertise in state-of-the-art gene transfer and editing, cellular immunological assays, experimental metastatic cancer models, multidimensional single cell analyses. Additional skills will be acquired also through the

computational analysis of the molecular data that will be performed in close collaboration with expert bioinformaticians involved in the AIRC Program Project.

References (max. 3)

1. Gorini F, Azzimonti L, Delfanti G, Scarfò L, Scielzo C, Bertilaccio MT, Ranghetti P, Gulino A, Doglioni C, Di Napoli A, Capri M, Franceschi C, Caligaris-Cappio F, Ghia P, Bellone M, Dellabona P, Casorati G, de Lalla C. Invariant NKT cells contribute to chronic lymphocytic leukemia surveillance and prognosis. Blood. 2017 129:3440-3451.

2. Cortesi F, Delfanti G, Grilli A, Calcinotto A, Gorini F, Pucci F, Lucianò R, Grioni M, Recchia A, Benigni F, Briganti A, Salonia A, De Palma M, Bicciato S, Doglioni C, Bellone M, Casorati G, Dellabona P. Bimodal CD40/Fas-Dependent Crosstalk between iNKT Cells and Tumor-Associated Macrophages Impairs Prostate Cancer Progression. Cell Rep. 2018 Mar 13;22(11):3006-3020