PROJECT 1

DoS: Anna Mondino

Title: TCR/CAR T cells and radiotherapy: time to team up against solid tumors

Curriculum: Basic and Applied Immunology and Oncology

Link to OSR/UniSR personal page: https://research.hsr.it/en/divisions/immunology-transplantation-and-infectiousdiseases/lymphocyte-activation/anna-mondino.html

Project description:

T lymphocytes have been defined as living drugs. Tumor-specific T cells can be purified and expanded from tumors or genetically engineered to express tumor-specific receptors, and re-infused in patients. Clinical responses have been documented mostly against hematological malignancies, while efficacy remains limited against solid tumors. Which are the constraints of tumor-T cell interaction within solid tumors? What limits therapeutic efficacy? Could conventional and more innovative strategies be used in combination? These are questions we have been tackling in the lab. We have exploited the genetic engineering of T cells with tumor-specific T Cell Receptor (TCR) or Chimeric Antigen Receptor (CAR) gene transfer for the treatment of solid tumors, and in particular against established adenocarcinoma of the prostate and pancreas adenocarcinoma liver metastasis in preclinical mouse models. In prostate cancer bearing mice, we found that engineered T cells per se are not sufficient to elicit tumor eradication, while in combination with local radiotherapy, deposition of pro-inflammatory cytokines or immune checkpoint blockers they can instruct therapeutic tumor debulking and long-term mice survival (Manzo and Sturmheit, Cancer Res. 2017; Elia et al. Cancer Res 2018; Gasparri A. Small, 2019; Basso, in preparation; Catucci et al, unpublished). In the case of prostate-confined radiation, we found that it to favor tumor permeability and supports local reactivation of engineered T cells. The mechanism underlying therapeutic activity remains in part to be understood. In addition, whether such approach also favors local antigen cross-presentation, ultimately turning a cold tumor into a “vaccine”, and whether endogenous T cells will be recruited and participate against metastatic disease remains to be investigated.
The student will be offered to ask these questions in preclinical mouse models, and study the phenotype and long-term persistence of TCR/CAR redirected T cells in combined therapeutic settings, define effects on tumor microenvironment and mechanism of rejection by knock down/inhibitors approaches. Concomitantly the student will have the opportunity to study immunoregulatory activity of local radiotherapy in prostate cancer patients by performing longitudinal multiparametric flow cytometry analyses of peripheral blood. This will not only help dissect the mechanism subtending radiotherapy efficacy, but also allow to isolate new tumor-reactive TCR to be later exploited in clinical trials (in collaboration with E. Ruggiero and C. Bonini).

Skills to be acquired by the student:

Research activity will expose the student to the genetic engineering of T cells and their molecular and functional characterization in mouse models and patients’ samples. Gene-expression analyses jointly with multiparametric flow cytometry and immunohistochemistry will allow the identification of T cells and of components of the tumor microenvironment. Peptide-driven T cell ex vivo expansion for the cloning of novel human TCR will be employed. The student will be responsible for experiments design and execution and engaged in result presentation in internal meeting first, and then in national and international meetings. Career promoting skills (i.e. scientific writing, public speaking, fellowship/travel grant application) will also be nourished.

References (selected up to 15)

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Unpublished data will be discussed at the time of interview.