PROJECT 1

DoS: Anna Mondino

Title: Unlocking tumors to TCR/CAR engineered T cells

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

Adoptive T cell therapy has become a promising option for cancer patients. While tumor-infiltrating lymphocytes were initially exploited as a source of tumor reactive lymphocytes, T cells genetically redirected to the tumor by tumor-specific T Cell Receptor (TCR) or Chimeric Antigen Receptor (CAR) gene transfer are now in clinical validation. Indeed, such T cells provide the unique opportunity to artificially overcome central and peripheral T cell tolerance rising the frequency of fully functional tumor-specific T cell populations and specifically point responses towards the patient's tumor. In the case of solid tumors, however, unfavorable immunosuppressive microenvironments remain recognized barriers to therapeutic efficacy. We found that targeting the tumor stroma (by mean of T cells redirected to an ubiquitously expressed minor histocompatibility antigen or a tumor vessel targeted TNF derivative) does empower TCR engineered T cells therapeutic potential (Hess Michelini, Cancer Res. 2010, Manzo, J. Immunol. 2011; Hess Michelini and Manzo, Cancer Res. 2013; Manzo and Sturmheit, Cancer Res. 2017; Elia et al. Cancer Res 2018; Gasparri A. Small, 2019; Petrozziello, In preparation; Basso, In preparation). Mechanistically, combinatorial strategies better evoked tumor infiltration and effector functions, resulting in acute tumor debulking and tumor-free survival. More recently, we also demonstrated that radiotherapy, currently adopted in 60% of patients with solid tumors also synergized with TCR engineered T cells in rejecting advanced mouse prostate adenocarcinoma in mice with autochthonous tumor development (Catucci et al, unpublished). We believe this is due to the ability or fractionated RT to promote immunogenic cell death, antigen release, endothelial cell activation and tumor infiltration by lymphocytes.
We wish now to take the concept further and investigate the possibility that the combination of local fractionated radiotherapy and TCR/CAR also instructs abscopal effect recruiting biological effectors outside the treatment field and resulting in regression of distant metastatic lesions.

Aim of the research project will be to set-up preclinical models of mouse and human metastatic prostate cancer and investigate the cellular and molecular mechanisms responsible for primary and metastatic tumor eradication. Experiments will involve a detailed characterization of T cell responses over the course of treatment in various anatomical district, to best define immunological correlated of observed clinical effects, exploiting both invasive (flow cytometry, immunofluorescence, immunohistochemistry) and non-invasive (magnetic resonance, bioluminescence) imaging techniques. Results will create knowledge on the events subtending therapy-driven tumor rejection and consensus for the clinical translation of the combined treatment.

Skills to be acquired by the student:

Research activity will expose the student to the genetic engineering and the functional and molecular characterization of primary T cells, to the setting of novel mouse models of tumor disease, to multiparametric flow cytometry and immunohistochemistry. Gene-expression studies will be adopted to study the consequence of radiotherapy on tumor cells, and associated stroma. A novel non-invasive MRIbased imaging will be developed. The student will be engaged in result presentation and encouraged to participate to national and international meetings. Career promoting skills (i.e. scientific writing, public speaking, fellowship/travel grant application) will also be nourished.

References (max. 3)

-Manzo T., T. Sturmheit, V. Basso, E. Petrozziello, R. Hess Michelini, … and A. Mondino. T cells redirected to a minor histocompatibility antigen instruct intratumoral TNF-α expression and empower adoptive cell therapy for solid tumors. Cancer Res. 2017 Feb 1;77(3):658-671.

- Elia, A.R. , M. Grioni, V. Basso, F. Curnis, M. Freschi, A. Corti,* A. Mondino,* and M. Bellone*. Targeting tumorvasculature with TNF leads effector T cells to the tumor and enhances therapeutic efficacy of immune checkpoint blockers in combination with adoptive cell therapy. Clinical Cancer Research, 2018 May 1;24(9):2171-2181. (*co-last). doi: 10.1158/1078-0432.CCR-17-2210.

- Mondino A., and T. Manzo. To remember or to forget: the role of good and bad memories in adoptive T cell therapy for tumors. Front. Immunol., 27 August 2020. https://doi.org/10.3389/fimmu.2020.01915

Unpublished data will be discussed at the time of interview.