

	PROPOSAL AS DIRECTOR OF STUDIES & RESEARCH PROJECT	MO-PHDMM-1 Rev. 06 del 04/03/2022
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PROJECT 1

DoS: Paolo Dellabona

Title: Functional enhancement of innate-like T cells by genetic engineering for the adoptive immunotherapy of metastatic cancers

Curriculum: BAIO

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):

The project will utilize experiments in vitro and in vivo. Mouse iNKT cells will be expanded and transduced in vitro with vectors encoding selected TCRs and CARs together genes encoding stimulatory cytokines and/or molecules that are being selected from published work. In addition, CRISPR-Cas9 gene editing will be utilized to eliminate the expression of a second set of published genes involved in restraining T cell functions in vivo. Engineered iNKT cells will be assessed in vitro for their enhanced tumor cell recognition and elimination, utilizing well established assays, and in vivo in realistic mouse models of liver metastases from syngeneic colon cancer. The anti-tumor functions of the various engineered iNKT cells will be investigate by deep profiling of tumor metastases with high dimensional flow cytometry and tissue multiplexing for spatially resolved proteomics or transcriptomics, to unravel the functional properties of each adoptively transferred cell product. The best performing genetic approach in mice will be investigate in human iNKT cells, which are highly conserved, in models of adoptive immunotherapy of human tumor xenotransplant in immunodeficient mice

Skills to be acquired by the student (Number of characters, including spaces: max 600):

The acquired skills will range from tissue culture and genetic modifications of mouse and human primary lymphocytes to immunological cellular assays, animal handling and modelling, high dimensional flow cytometry and spatially resolved omics, including hints on computational analysis.

References (max. 15)

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;22(11):3006
3. Consonni M, Garavaglia C, Grilli A, de Lalla C, Mancino A, Mori L, De Libero G, Montagna D, Casucci M, Serafini M, Bonini C, Häussinger D, Ciceri F, Bernardi M, Mastaglio S, Bicciato S, Dellabona P, Casorati G. Human T cells engineered with a leukemia lipid-specific TCR enables donor-unrestricted recognition of CD1c-expressing leukemia. *Nat Commun*. 2021 Aug 11;12(1):4844.