PROJECT

Supervisor:	_____ Monica Casucci _____
Title:	Integrated CAR-TCR T-cell engineering for durable immunotherapy in colorectal cancer
Curriculum:	Molecular Medicine: Basic and Applied Immunology and Oncology
Link to the personal page of the University or relevant hospital site website:	_____https://research.hsr.it/en/divisions/immunology-transplantation-and-infectious-diseases/innovative-immunotherapies/monica-casucci.html _____

Description of the Project (max 3,000 characters including spaces)

Background/gap of knowledge

Colorectal cancer (CRC) is a leading cause of cancer mortality and remains largely refractory to immunotherapy due to antigenic heterogeneity and a highly immunosuppressive tumor microenvironment. These barriers have prompted the development of T cells engineered with exogenous receptors, which offer distinct but complementary advantages. Chimeric antigen receptors (CARs) induce potent effector functions but are limited to extracellular targets and may exhibit reduced persistence, whereas T-cell receptors (TCRs) recognize a broader repertoire of antigens, including intracellular targets, and generally persist longer, although their HLA restriction limits applicability. Importantly, both approaches are vulnerable to antigen escape in CRC and other solid tumors. Casucci's group has developed a CAR targeting the CRC-associated antigen CDH17, while the Ruggiero and Bonini laboratories have generated HER2-specific TCRs, providing a strong foundation for CRC-targeted T-cell engineering. However, how to effectively combine these complementary platforms to overcome antigen escape and improve therapeutic durability in CRC remains undefined.

Rationale and hypothesis

We hypothesize that the combined or integrated use of CAR- and TCR-engineered T cells will enhance tumor control by reducing antigen escape and improving functional persistence, thereby overcoming key limitations of single-modality therapies.

Objectives and specific aims

The general aim of this project is to develop and optimize a novel cell-based therapy for CRC by exploiting the complementary functions of CDH17-CAR and HER2-TCR, and to define the optimal strategy between combination and dual-receptor engineering.

Specific aims are:

1) to assess the efficacy, safety, and functional interplay of CDH17 CAR-T and HER2 TCR-T cells administered alone, simultaneously, or sequentially in preclinical CRC models;

2) to generate and validate dual-receptor T cells co-expressing CDH17-CAR and HER2-TCR, and to compare their performance with combinatorial approaches in terms of antitumor activity, persistence, and cellular fitness.

Expected outcomes

The project has the ambition to develop novel highly potent therapies for CRC and to provide mechanistic insights into the cooperative interplay between CARs and TCRs.

Skills that the student should acquire (max. 600 characters including spaces):

The project will develop within a collaborative network involving the Casucci, Ruggiero and Bonini labs. I will coordinate joint supervision and ensure constant interaction among Units, providing an excellent PhD training environment.
Hard skills: vector design; gene editing; production of engineered T cells and functional testing in vitro and in advanced animal models; use of high-throughput analyses.
Soft skills: critical literature review; project design/management; data presentation; scientific communication in meetings, conferences and reports; thesis and manuscript writing.

References (max. 15)

Greco B, El Khoury R et al. SCI TRANSL MED 2025. Systemic delivery of cadherin 17-specific CAR T cells allows effective and safe targeting of colorectal cancer liver metastases.

Potenza A, Balestrieri C et al. GUT 2023. Revealing and harnessing CD39 for the treatment of colorectal cancer and liver metastases by engineered T cells.

Ruggiero E et al. SCI TRANSL MED 2022. CRISPR-based gene disruption and integration of high-avidity, WT1-specific T cell receptors improve antitumor T cell function.

Bove C, J IMMUNOTHER CANCER 2023. CD4 CAR-T cells targeting CD19 play a key role in exacerbating cytokine release syndrome, while maintaining long-term responses.

Arcangeli S, Bove C, Mezzanotte C, et al. J CLIN INVEST 2022. CAR T-cell manufacturing from naive/stem memory T-lymphocytes enhances antitumor responses while curtailing cytokine release syndrome.