Universidad de Navarra
Facultad de Ciencias

MASTER'S DEGREE IN BIOMEDICAL RESEARCH
Research Project Proposal
Academic year 2024-2025

Project Nº 28

Title: Senescent T-cell biomarkers to select the best T cell Receptors for T-cell Therapy

Department/ Laboratory *Laboratory where the project will be carried out indicating Department, Area, Faculty, CUN, CIMA etc.*
Inmunología e Inmunoterapia/Terapia celular adoptiva (CIMA)
Biología y terapias de ARN/ARN no codificante (CIMA)

Director 1: Marta Montes
Contact: *mmontesr@unav.es*
Codirector: *Sandra Hervás*
Contact: *mshervas@unav.es*

Summary *Short summary of the project with a* ***maximum extension of 250 words****, including the goals and the methodology that will be used*

A promising strategy for cancer treatment is Adoptive T cell Therapy (ACT) using T cells genetically engineered with a tumor-specific T-cell receptor (TCR) that allows them to recognize and destroy tumors. One of the challenges TCR-T cell therapy is facing, is to find TCRs that prevent the exhaustion of T cells, so that they can exert their antitumor action for a longer time. From transcriptomic data (single cell RNA&TCRseq) that we have generated, we have identified a genetic expression signature (GAP signature) that allows to distinguish TCRs that perform well in ACT (GAP-TCR, Good ACT Performance) from those that perform poorly (P) in ATC (PAP-TCR). TILs presenting GAP-TCRs present gene expression patterns related to metabolic fitness, while TILs expressing PAP-TCRs are exhausted T-cells that present a signature of overactivation. We hypothesized that (i) TILs presenting PAP-TCRs are senescent T cells and (ii) that the expression of PAP-TCRs in T cells may make them more likely to become exhausted/senescent when encountering the tumor cell. The expression of GAP-TCR may allow T cells to be more competitive in attacking the tumor, by preventing their early senescence. The addition of senescence hallmarks to the GAP signature could help selecting the best TCRs for ACT.

Aim 1- Investigate whether TILs presenting PAP-TCRs express senescence markers by analyzing the available scRNA&TCRseq data.

Aim 2- Evaluate senescence and the metabolic state of T cells genetically modified with either GAP-TCRs or PAP-TCRs in *in vitro* and *ex vivo* assays, by flow cytometry, RT-PCR and functional studies.

yes	x
no	

Does the project include the possibility of supervised animal manipulation to complete the training for animal manipulator? YES