



MASTER'S DEGREE IN BIOMEDICAL RESEARCH

Research Project Proposal

Academic year 2024-2025

Project Nº 05

Title: Validation of factors improving CAR T cell function combining CRISPR-based editing tools and next generation sequencing.

Department/ Laboratory: Immune Therapy group (lab 1.04), Hemato-Oncology Program, Cancer Division. Cima Universidad de Navarra.

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Summary

Adoptive cell therapy strategies based on T lymphocytes engineered with chimeric antigen receptors (CAR T cells) have evolved to become a real therapeutic option for patients with certain B cell malignancies. However, CAR T therapies still present several limitations, including lack of long-term efficacy and treatment associated toxicities, and the molecular mechanisms responsible of these limitations are not yet fully understood. In this sense, combination of next generation sequencing with gene editing technologies, such as CRISPR systems, have transformed the biological approach to understanding the molecular mechanisms associated with different biological processes.

Thus, the **main objective** of this project is to **modulate relevant factors** in CAR T cells, by using **CRISPR technologies**, and **evaluate** the effect of their modulation in the **functionality of** CAR T therapies. In this project we will generate primary human CAR T cells deficient in each of the selected factors using CRISPR systems, that will be characterized both *in vitro* and *in vivo* against tumoral cells. *In vitro* lytic capacity of CAR T cells will be measured by standard cytotoxic assays using a luminescence-based method. Cytokine production will be measured by ELISA and phenotypic analysis will be performed by flow cytometry. Finally, the *in vivo* antitumor efficacy of CAR T cells will be evaluated in MM xenograft models generated in immunodeficient NSG mice inoculated with MM cell lines expressing GFP-Luc.

yes	X
no	

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