Universidad de Navarra
Facultad de Ciencias

MÁSTER EN INVESTIGACIÓN BIOMÉDICA
Research Project Proposal
Academic year 2022-2023

Project Nº 15

Title: *Vaccination to improve the efficacy of CAR-T cells sin solid tumors*

Department/ Laboratory
Laboratorios de "Terapia celular adoptiva" y "Terapia Génica para Cáncer" del Programa de "Inmunología e Inmunoterapia" y "Terapia Génica", respectivamente. Centro de investigación Médica Aplicada (CIMA).

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Summary

Chimeric antigen receptor (CAR) T cells (CAR-T) represent a revolutionary treatment for hematological tumors but their efficacy in solid tumors has not been yet supported. The efficient activation and expansion of CAR-T cells *in vivo* is key for the success of CAR-T therapy. Both phenomena are highly dependent on the recognition of the tumor antigen (Ag). For solid tumors, CAR-targeted Ag (CAR-Ag) recognition occurs exclusively in the tumor microenvironment (TME). However, the immunosuppressive TME prevents the efficient activation and expansion of CAR-T cells. We believe that off-tumor recognition of CAR-Ag could exert a boosting effect and substantially improve the efficacy of CAR-T therapy in solid tumors. This could be safely achieved with companion vaccines expressing the CAR-Ag. The mRNA molecule is a versatile drug class that can encode proteins with therapeutic interest, including tumor Ags. Self-amplifying (sa)RNA is a new platform which uses similar technology to mRNA but with the added ability to self-amplify, thereby resulting in higher protein levels per dose. Most saRNA vaccines are based on the genomic RNA of an alphavirus. Our group has very broad experience in the use of alphavirus vectors derived from Semliki Forest virus (SFV) to express immunotherapeutics. The goal of this project is to study the therapeutic effect of CAR-T cells in combination with SFV-derived vaccines encoding for the CAR-Ag.
For that purpose, the following partial objectives are proposed: (1) Production of SFV-derived vaccine expressing the CAR-Ag. Three different vaccines will be tested: the SFV-saRNA, either packaged into (i) pseudoviral particles or (ii) conjugated to nanoparticles; and (iii) a plasmid containing the SFV vector sequence (SFV-DNA) in such a way that the SFV-saRNA can be transcribed in vivo; (2) Engineering murine T-cell lines to express the CAR; (3) Testing the ability of CAR-T cell s to be boosted by SFV-derived vaccines; (4) Testing the antitumoral activity of the CAR-T-cell/vaccine combination in preclinical mouse solid tumour models.
The project will involve the use of many different techniques, including Molecular Biology, cell culture, virus production, analysis by flow cytometry, immunological techniques, animal models of cancer, monitorization of immune responses etc.

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

yes	√
no	