Universidad de Navarra
Facultad de Ciencias

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

Project Nº 35

Title: *Inducible CAR-T cells to fine tune the antitumor activity reducing toxicity*

Department/ Laboratory
Immunology and Immunotherapy program.
Lab 3.02. CIMA.

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Summary

Chimeric antigen receptor CAR-T cell therapy is a revolutionary new pillar in cancer treatment. Although treatment with CAR-T cells has produced remarkable clinical responses in B cell leukemia, many drawbacks limit the therapeutic efficacy of CAR-T cells in solid tumors. The identification of specific tumors antigens in solid tumors is a challenge since they are often expressed on normal tissues at varying levels, resulting in "on-target, off-tumor" toxicity, a direct attack of healthy tissue by CAR-T. Therefore, antigen selection and control of CAR expression is crucial in CAR design to not only ensure therapeutic efficacy but also to limit toxicity. Tet-On 3G is the third generation of tetracycline-inducible gene expression systems, which could reversibly turn-on or turn-off the gene expression using doxycycline (Dox). In this master project, we will investigate the Tet-On 3G system as a choice to regulate the expression of CAR in T cell, both in vitro and in vivo to minimize the toxicity while improving antitumor efficacy.

Methodology:
Based in the already available and validated CAR constructs, the candidate will generate a retroviral vector containing the Tet-On 3G inducible system to express the CAR. Then, Tet-CART cells will be generated and the optimal dose and dynamics of Dox-regulated CAR expression will be determined. Subsequently, both in vitro and in vivo therapeutic effects of Tet-CART cells will be evaluated.
All in all, the candidate will acquire the following expertise: **(i)** T cell isolation and culture. **(ii)** Retrovirus production. **(iii)** T cell infection. **(iv)** Functional T-cell assay: ELISPOT, ELISA, Flow Cytometry, cytotoxicity. **(v)** Efficacy in vivo experiments by using immunocompetent tumor models.

yes	x
no	

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