Research Project Proposal
Academic year 2020-2021

Máster en Investigación Biomédica

Project Nº 20

Title:
Improving CART cell therapies for hematological malignances: from innovative CAR designs to modulation of molecular mechanisms.

Department/ Laboratory: *Lab 1.01, Hemato-Oncology Department, CIMA Universidad de Navarra*

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Summary

Chimeric antigen receptors T (CART) cells are emerging as the most innovative and promising advanced immunotherapy for cancer treatment. CART therapies have shown spectacular efficacy in acute lymphoblastic leukemia, leading to the approval of two commercial products, Kymriah and Yescarta. However, CART therapies have not been proved to be as efficacious for other hematological diseases, resulting on a significant number of non-responder patients and a significant rate of relapse.

Several determinants of response have been described, including robust *in vivo* expansion and a long-term persistence of CART cells, since most of the clinical trials have reported poor CART cell persistence in non-responder/relapsed patients. Several factors can influence CART cell expansion/persistence, including the molecular design of CARs, the patient preconditioning, *ex vivo* culture conditions, the tumor microenvironment, or host immune responses against the cellular infusion product.

The recent development of novel sequencing technologies, that allow integrated and unbiased analysis, offers a valuable tool to *understand the mechanisms promoting CART cell expansion and persistence that are not yet fully understood*.

In this project we will generate CART cells with different designs, from patients with different disease status and/or cultured in different conditions, that will be transcriptomic and immunophenotypically characterized at single-cell level. These analyses would help us to *identify specific subpopulations* that might play essential roles in CART persistence and *to identify possible targets*, that will be validated by loss-of-function experiments using CRIPSR/Cas9 systems.

yes	**X**	**Does the project include the possibility of supervised animal manipulation to complete the training for animal manipulator?**
no		