Research Project Proposal
Academic year 2019-2020

Project Nº 23

Title:
Mechanisms of long-term CART cell persistence for improved therapeutic efficacy.

Department/ Laboratory
Laboratory 1.01. Regenerative Medicine Program. CIMA Universidad de Navarra.

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Summary

Chimeric antigen receptors T (CART) cells are emerging as the most innovative and promising advanced therapy for cancer treatment. However, despite the spectacular efficacy observed in acute lymphoblastic leukemia, CART therapies have not been proved to be as efficacious for other tumours, resulting on a significant number of non-responder patients and a significant rate of relapse. In this regard, a robust *in vivo* expansion and a long-term persistence of CART cells are considered critical for a durable clinical remission, since most of the clinical trials have reported poor CART cell persistence in non-responder/relapsed patients. Several factors can influence CART cell persistence, including patient preconditioning, *ex vivo* culture conditions, development of T cell exhaustion, or host immune responses against the cellular infusion product. Moreover, the molecular design of CARs strongly influences CART cell expansion and persistence, being critical the intracellular signaling domain (ICD) that transmits activation signals. 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 aim to analyze at single-cell level the differences between CART cells signaling through different ICD, such are CD28, 4-1BB or their different combination. For that purpose, we will generate different CART cells that will be transcriptomic and immunophenotypically characterized by CITE-seq. These analyses would help us to *identify specific CART subpopulations* that might play essential roles in persistence and *to identify possible targets*, that will be validated by loss-of-function experiments using CRIPSR/Cas9 systems.

yes	**X**
no	

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