Research Project Proposal
Academic year 2021-2022
MÁSTER EN INVESTIGACIÓN BIOMÉDICA

Project Nº 23

Title: *Humanization of high-affinity T cell receptors (TCR) developed in nontolerant nonhuman hosts to exploit TCR-therapy targeting shared tumour antigens*

Department/ Laboratory *Program of Immunology and Immunotherapy (CIMA)*

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Summary:

A new immunotherapy for cancer is the adoptive T-cell therapy. In these treatments, patients are treated with their own T cells, which have been genetically modified to express receptors capable of recognizing tumor antigens. Among these receptors is the physiological molecule used by T cells, the "TCR", which recognizes tumor antigens presented by the patient's HLA molecules. An effective method to identify "tumor-specific" TCRs is to vaccinate mice expressing human HLA molecules with human tumor antigens (HLA-transgenic mice). Lymphocytes from these mice are used to identify tumor-specific TCRs, which are then expressed in the patient's lymphocytes. Using this system, our laboratory has identified a TCR capable of recognizing Glypican-3 (GPC3), an antigen present in various types of solid tumors. Although the TCRs identified in this way are functional in patients, the molecule itself comes from mice and this may generate a xenogenic response that might preclude their clinical use. Through a process known as "humanization", it is possible to humanize murine sequences. However, the humanization of mouse TCRs is still little explored. In this project, we propose to humanize the murine GPC3 TCR using a methodology assisted by molecular modelling. The humanized TCR sequences will be cloned (Golden-Gating assembly) in retroviral vectors and retrovirus will be produced to transduced human T cells. Genetically modified T cells expressing the humanized TCRs will be tested for their ability to recognize tumor cells, both in vitro (using Flow-cytometry, ELISPOT, and real-time cytotoxicity assay among other assays) and in vivo (using NSG mouse models).

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