Research Project Proposal
Academic year 2020-2021

Máster en Investigación Biomédica

Project Nº 48

Title: Anti-drug-antibodies (ADA) as a mechanism of acquired resistance in cancer immunotherapy

Department/ Laboratory: Immunology and Immunotherapy Program, Lab 3.0.6, CIMA

Director 1 *Miguel Fernández de Sanmamed*
Contact: *msanmamed@unav.es*
Codirector: *Beatriz Moreno Bruna*
Contact: *bmbruma@unav.es*

Summary

Cancer immunotherapy, mostly based in PD-1/PD-L1 pathway blockade agents, have revolutionized the way to treat solid tumors. However, primary resistance is a common event in cancer patients, and among responders a significant fraction relapse with drug-resistant disease, what is known as acquired resistance. Causes of acquired resistance are typically considered related with tumor immune edition (i.e. B2M loss, immunogenic epitopes silencing) or the induction of compensatory immune-inhibitory mechanisms (i.e. TIM-3 pathway up-regulation, LAG-3 pathway up-regulation, etc…). Here we propose that a potential mechanism of anti-drug resistance may be the direct development of anti-drug antibodies (ADA) against anti-PD-(L)1 agents. This is more likely and well reported in the case of mutated anti-PD-L1 mAbs as atezolizumab, which has been overdosed expecting that after several doses neutralizing ADA may limit the activity of this compound in 40% of the patients. We hypothesized that even with the use of fully humanized mAbs as nivolumab or pembrolizumab, ADA can be developed in patients with a long exposure. We have collected plasma samples at baseline and at the moment of CT-scan assessment in 80 non-small lung cancer and 50 urothelial cancer patients treated with anti-PD-(L)1 agents. Our plan is to assess the ADA levels in atezolizumab, nivolumab and pembrolizumab treated patients by ELISA and study the association of these levels with response and acquired resistance of these patients. These type of study will explore the relevance and potential impact of ADA in cancer immunotherapy based in anti-PD-(L)1 mabs.

yes	**X**
no	

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