Research Project Proposal
Academic year 2018-2019

Project Nº 35

Title: *Humanised-mouse models to implement immunotherapy of cancer*

Department/ Laboratory *Department of Immunology and Immunotherapy, CIMA*

Director 1 *Miguel Fernández de Sanmamed Gutiérrez*
Contact: *msanmamed@unav.es*
Codirector: *Ignacio Melero Bermejo*
Contact: *imelero@unav.esl*

Summary Immunotherapy based in anti-PD therapies is revolutionizing treatment of multiple cancers, markedly prolonging survival with manageable safety. However**,** despite this remarkable success, more than 60% of patients show resistance. Thus, we need to better understand the mechanism of action and resistance of these therapies to improve their use in clinical oncology. One of the main limitations in evaluating and developing new immunotherapies is the absence of suitable animal models in which human immune responses against cancer can be interrogated. Another important limitation is the difficulty of obtaining patient tumour biopsies, which are essential to clarifying our understanding of the mechanisms behind these drugs. We propose to co-engraft human CD34+ cells and tumour xenografts from cancer patients in a next-generation, immunodeficient mice, termed MISTRG. These mice are optimized to support the development and maintenance of a fully human hemato-lymphoid system from human CD34+ cells, with the capacity to infiltrate subcutaneous co-engrafted tumours: humanised-PDX model. This approach will allow us to recapitulate the main features of the patient tumour microenvironment (TME), and study the human tumour and immune cell interactions in a physiologically relevant system. We plan to characterize the TME cellular components before and after PD-pathway blockade using a novel single cell high-dimensional technology known as mass cytometry (CyTOF) combined with a spatial resolution technology known as multiplex-immunofluorescence. We will then validate our results in a clinical settings by longitudinally studying the changes in patients' tumours as they undergo therapy. Our studies will focus on specific immune compartment changes (function and location) and expression of inhibitory pathways outside of the canonic PD-pathway. We hope to identify primary and acquired mechanisms of resistance to anti-PD-treatment. This project will also serve as a platform to experimentally study combinatorial therapies to that may overcome identified resistance mechanisms. A better understanding of these mechanisms will lead to rational designs of combinatorial treatments and biomarker studies to improve the success of new immunotherapies.

yes	**X**
no	

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