Universidad de Navarra

Máster en Investigación Biomédica
Facultad de Ciencias

Research Project Proposal
Academic year 2015-2016

Project Nº 14
Title: Blockade of immunoregulatory molecules in dendritic cells to improve antitumor vaccine efficacy
Department/ Laboratory Laboratory of Experimental Immunology, Program of Immunology and Immunotherapy, CIMA.
Director 1 Pablo Sarobe **Contact:** psarobe@unav.es **Codirector:** Diana Llopiz **Contact:** diallo@unav.es
Summary Despite encouraging results in preclinical models, antitumor vaccines administered to cancer patients in the last years have yield poorer results than expected. Immunosuppressive environment described in these individuals may be partly responsible for these effects. Dendritic cells (DC), professional antigen presenting cells responsible for T cell activation and a key population in vaccine functions, are inhibited by this environment. We have demonstrated that blockade of some of these factors by using peptides or antibodies increases DC functions and as a consequence, stronger immune responses are induced. Thus, the goal of this project is the blockade/inhibition of immunosuppressive elements triggered by the tumor and operating at the level of DC to enhance their immunostimulatory functions. As a novelty with our previous approach, in this project we will design viral vectors encoding shRNA molecules targeting relevant immunosuppressive molecules together with tumor antigens. Vectors will be produced and used to transduce DC. Phenotypical and functional properties of transduced DC will be tested in vitro by using techniques of gene expression, flow cytometry and functional antigen presentation assays. DC transduced with selected vectors (or directly the vectors) will be administered to mice as vaccines to analyze their immunogenicity in vivo. Finally, therapeutic antitumor effect of most immunogenic vaccines will be tested in relevant tumor models, where vaccine efficacy and their underlying immunological mechanisms will be analyzed. **References** -“Helper cell-independent antitumor activity of potent CD8+ T cell epitope peptide vaccines is dependent upon CD40L”. Llopiz D,et al Oncoimmunology. 2013 Dec

1;2(12):e27009.

- "Enhanced T cell responses against hepatitis C virus by ex vivo targeting of adenoviral particles to dendritic cells" Echeverria I, et al. Hepatology. 2011 Jul;54(1):28-37. doi: 10.1002/hep.24325.

- "Adjuvant combination and antigen targeting as a strategy to induce polyfunctional and high-avidity T-cell responses against poorly immunogenic tumors" Aranda F et al. Cancer Res. 2011 May 1;71(9):3214-24. doi: 10.1158/0008-5472.CAN-10-3259.

POSSIBILITY OF PhD

YES*

* (PhD grant required)