ImmunoTools *special* Award 2014

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"TOWARDS MORE ACTIVE ROLES OF GLYCO-CONJUGATES IN CANCER IMMUNOTHERAPY"

Currently, immunotherapy-based approaches in cancer are regretfully underestimated as a consequence of the sophistication of this biological system that requires a deeper understanding. Immunotherapy has, however, an enormous potential in cancer treatment. Supporting this idea, two recent clinical trials in cancer therapy based on bypassing the mechanisms of tumor-immune escape (targeting of PD-1 and CTLA-4) gave some incipient encouraging results (1-3).

Our laboratory is focused on obtaining a better understanding of multi-molecular interactions involved in tumor-associated immune activation and/or tolerance in prostate cancer (PCa), information that is required in order to identify new efficient therapies for this disease. In this respect, we have three research projects carried out by different PhD students. One of our projects (submitted for this award) is based upon the observation that cell transformation is characterized by aberrant glycosylation and lectin expression and proposes to take advantage of such glyco-signatures as critical potential targets for new immunotherapeutic treatments for PCa.

The murine TRAMP-C1 experimental model of PCa is the basis of this project. A major concern in the construction of this model refers to the evaluation of the **whole microenvironment**, reason why, when possible, biological tests are performed in an **entire animal**. In this respect, we have standardized an experimental model that is currently used in our laboratory that consists on the *s.c.* injection of TRAMP-C1 cells in a syngenic graft system. Our interdisciplinary approach combines molecular and cellular biology, biochemistry and *in vivo* experimentation, disciplines that are integrated in a logical way in order to achieve the main goals of the project, which are:

First, to determine whether lectins could be proposed as new immunotherapeutic targets in cancer. Some lectins are over-expressed specifically by tumors and as well they can be proposed as tumor associated antigens (TAA). We designed *in silico* a battery of lectin-derived peptides capable of binding MHC class I (Kb and Db). In a first approach to evaluate their biological properties, these peptides are used to immunize C57BL/6 mice. Specific anti-tumor immune responses are followed up by analyzing different biological parameters. We are actually evaluating parameters of early (CD69) and late (CD44) activation markers in $CD8^+$T cell as well as their cytotoxic function (through determination of granzyme, perforin, FAS, CD107). This is performed by flow

cytometry (surface and intracellular staining), *in vivo* cytotoxicity and cytokine production and *in vitro* cytokine determination by ELISA in cultured cells. Altogether, these results will determine whether the proposed intervention based on lectins as a TAA is capable of being used to induce specific immunotherapeutic approaches.

Second, we will study the ability of glycans to modulate tumor-specific immune responses. Our project puts forward the original proposition about how certain glycan-mediated modifications may be an artificial mean to modulate the ability of TAA-derived peptides (defined in previous aim) to induce and activate an effective and specific anti-tumor immune response. Methodological procedures are similar to the first aim.

Last but not least, the long-term goal of this project encompasses the clinical translation of basic immunology findings that could impact on the survival of patients with PCa. For this reason our results will be further validated **using patient samples** to assess the translational properties of our conclusions. Therefore, we have set up collaboration with clinicians to get human samples (biopsies and blood from patients) and their point of view about the findings. In this respect, the current proposal is designed to be as simple as possible to ensure an easy translation into the clinic, with a **high probability of near-term patient benefit**. In summary, our results will significantly contribute to the **design of novel anticancer therapeutic strategies** which, in combination with current treatments**, will be of paramount clinical benefit in men with advanced prostate cancer and hopefully such knowledge would be applicable to others cancers.**

Our group of research was created in 2009 and, as a young group, our major goal is to grow harmoniously, we endeavor to participate in the formation of high quality human resources, promoting national and international scientific collaborations trying to shed some light on several aspects we consider relevant in the field of tumor immunology. We hope ImmunoTools will regard our group as fitting the requirements to obtain this Award that would be of great benefit to our research.

[1] Hodi FS, O'Day SJ, McDermott DF, *et al.* Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010; 363: 711-23.
[2] Brahmer JR, Tykodi SS, Chow LQ, *et al.* Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med 2012; 366: 2455-65.
[3] Topalian SL, Hodi FS, Brahmer JR, *et al.* Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 2012; 366: 2443-54.

ImmunoTools *special* AWARD for **Diego Laderach** includes 24 reagents

PE - conjugated Annexin V,

APC - conjugated anti-human CD8,

FITC - conjugated anti-mouse isotype control IgG2b,

PE - conjugated anti-mouse CD4, CD8a, CD11b, CD25, CD44, CD62L, isotype control IgG2b,

APC - conjugated anti-mouse CD4, CD8a, CD11b, Gr-1, isotype control IgG2b,

recombinant mouse cytokines: rm Flt3L/CD135, rm GM-CSF, rm IL-2, rm IL-4, rm IL-7, rm IL-10, rm IL-15, rm sCD40L/CD154, rm TNFa, rm VEGF

DETAILS more AWARDS