Research Project Proposal
Academic year 2019-2020

Project Nº 25

Title: *New immunomodulatory combinations against lung adenocarcinoma (LUAD) according to the mutational status of KRAS oncogene. Study of new biomarkers of response to anti-PD-1 therapy.*

Department/ Laboratory
Department of Oncology (CUN)/Laboratorio de Marcadores predictivos de respuesta (CIMA). 2.01

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Summary

In this study we aim to demonstrate that the lack of the Id1 gene in different murine lung adenocarcinoma (LUAD) cell lines has an immunostimulatory role that favours the activation of different immune populations in co-culture. In addition, we intend to study *in vivo*, in several murine models, that the inhibition of Id1 expression, both in the tumor immune microenvironment and in tumor cells (by silencing Id1 using short hairping RNA or by using a small inhibitory molecule), combined with PD-1 blocking (using specific monoclonal antibodies) and MEK1/2 (with last-generation inhibitors) represents a synergistic antitumor strategy in *KRAS* driven LUAD. Furthermore, we want to explore the influence not only of the *KRAS* status but also the role of concurrent mutations in *TP53* and *LKB1/STK11* in the clinical evolution of a prospective series of 50 consecutive patients with advanced LUAD treated with monoclonal antibodies against PD-1. We also plan to study the predictive role of response to PD-1 inhibitors by analyzing the combined expression, by immunohistochemistry, of Id1 and PD-L1 in the tumor samples of those patients and their correlation with the presence or absence of mutations in *KRAS* and the concurrence of those, with genomic alterations in *TP53* and/or *LKB1/STK11*. Other potential predictive biomarkers such as the presence of TIL and the combined expression of other immune activation markers (CD4, CD8, CD3, FOXP3, CD68, PD-1, PD-L1, CD11b, CD56 and CD16), will be investigated by multispectrum immunophenotyping as well as the role of secreted soluble cytokines. Finally, we will investigate the mechanisms by which Id1 acts blocking the activation of the immune response, by studying *in vitro* its role in peripheral blood lymphocytes and antigen-presenting cells.

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