Research Project Proposal
Academic year 2019-2020

Project Nº 20

Title: *Modulation of innate immnune response to potentiate lung cancer immunotherapy*

Department/ Laboratory *Program in Solid Tumors (CIMA).*

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Summary

Immunotherapy based on PD-1/PD-L1 blockade has emerged as a potent tool for the treatment of lung cancer. These drugs remove the inhibition of T-cell activation and restore antitumor immune responses. However, PD-1/PD-L1 inhibition is not capable of reversing all resistance mechanisms, and a proportion of patients do not respond adequately to PD-1/PD-L1 immunotherapies. Our major goal in the past years has been the study of the mechanisms of complement activation in lung cancer. We have demonstrated that complement C5a, through its receptor C5aR1, favors the formation of an immunosuppressive microenvironment that promotes tumor progression. Recently, we have demonstrated in preclinical models of lung cancer that the pharmacological blockade of C5a synergizes with PD-1 blockade to inhibit lung cancer progression (Ajona et al. Cancer Discovery 2017), and prevents the metastatic spread (Ajona et al. AJRCCM 2018). In this context, a Phase I/II study (STELLAR-001) is now evaluating the safety and efficacy of combined inhibition of C5a/C5aR1 and PD-1/PD-L1 signalling in patients with advanced solid tumors. We here propose a project in which the mechanisms that mediate the effect of C5a/C5aR1 in lung tumors will be studied. Moreover, we will dissect the immunological effects of the combined therapy anti-C5a/PD-1 in syngeneic *in vivo* models in order to optimize this therapy and overcome the resistance mechanisms. This project will contribute to a better knowledge of the interaction between cancer and the innate immunity, will provide insights into new therapeutic targets, and may provide support for the development of new therapies against lung cancer.

yes	**X**
no	

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