# Research Project Proposal
Academic year 2018-2019

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| **Project Nº 25** | |
| **Title:** *Modulation of the innate immune response to potentiate the antitumor activity of immunotherapy against lung cancer* | |
| **Department/ Laboratory:**<br>Program in Solid Tumors. Laboratory of Biomarkers and New Therapies. CIMA | |
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**Summary**. Immunotherapy based on checkpoint inhibitors has emerged as a potent tool for the treatment of lung cancer, the leading cause of cancer deaths throughout the world. Monoclonal antibodies that inhibit the interaction between PD-1 and its ligands have shown the most compelling clinical results. However, their effectiveness is limited by the generation of a tumor immunosuppressive microenvironment. One of our main research interests 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 by the recruitment and activation of myeloid-derived suppressor cells (MDSCs). In this context, we have recently demonstrated that the pharmacological blockade of C5a significantly increases the antitumor capacity of a treatment based on PD-1 blockade in preclinical models of lung cancer (Ajona et al. Cancer Discovery 2017), and that C5aR is involved in the metastatic spread of lung cancer cells (Ajona et al. AJRCCM 2018). We here propose a project in which the mechanisms that mediate the effect of C5a/C5aR1 in lung tumors and their environment will be studied. At the same time, we will dissect the immunological effects of the combined therapy anti-C5a/PD-1 in syngeneic in vivo models with the goal to optimize this therapy and overcome the resistance mechanisms. Finally, we will extent these studies to other complement effectors. 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 will establish the proof of concept for the development of new therapies against lung cancer.Our research in this field is supported by several national and international institutions, including the Spanish Ministry of Health (FIS and CIBERONC), the Australian National Health and Medical Research Council, and the Spanish Association Against Cancer (AECC).

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| **yes** | X |
| **no** | |

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