**Research Project Proposal**
Academic year 2018-2019

**Project Nº** 48

**Title:** *ANTITUMOR ACTIVITY OF ID1, MEK1/2 AND PD-1 COMBINED BLOCKADE IN A KRAS-DRIVEN NON-SMALL CELL LUNG CANCER MODEL*

**Department/ Laboratory** *Department of Oncology, New Therapuetic Targets Laboratory, Laboratory 2.01, CIMA*

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**Summary**

*Anti-PD-1/PD-L1 therapies have revolutionized NSCLC treatment. Nonetheless, there is still a large fraction of patients that do not benefit from such interventional strategies, and for those who can be treated there are currently no accurate biomarkers of response. In addition, combination of distinct regulators of the immune system could unveil synergistic therapeutic approaches in NSCLC. Previous work from our group indicates that Id1 (Inhibitor of Differentiation 1) tumor expression is an independent prognostic factor in lung adenocarcinoma (Ponz-Sarvisé et al. Clin Cancer Res 2011). Moreover, Id1 loss notably reduces metastasis of NSCLC cells (Castanon et al, Can Letters 2017). In addition, NSCLC harboring KRAS mutations are more sensitive to Id1 inhibition and FOSL-1 may play a crucial role (Roman, et al. Cancer Research 2018, in press). FOSL-1 has been also shown to confer poor prognosis to KRAS-driven NSCLC patients as demonstrated in other work from collaborators in our same institution (Vallejo et al, Nat Commun, 2017). Moreover, KRAS mutations have been postulated as a predictive factor of response to anti-PD-1 blockers and may benefit from MEK1/2 inhibition, as reviewed in a recent paper by our group (Roman M et al, Mol Cancer 2018). Our main hypothesis is that Id1 and PD-1 would act in a synergistic fashion to favor a suppressive immune system environment and, therefore, their concomitant inhibition would lead to a greater anti-tumor response in NSCLC. Silencing of Id1 expression will be performed in Lewis Lung Carcinoma cells (LLC cells) in this experiment by doxycycline inducible- short hairpin RNA or constitutive-short hairpin RNA, and LLC Ctrl clones (controls).* In this study, wild type C57/BL6 (Id1+/+) mice and Id1-deficient (Id1-/-) mice with the same genetic background will be employed. A subcutaneous as well as a metastatic mouse model will be used. Multispectral immunophenotyping, transcriptomic analysis and analysis of immunomodulatory circulating cytokines by Luminex, will be also performed.

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

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