Universidad de Navarra

Máster en Investigación Biomédica
Facultad de Ciencias

**Research Project Proposal**
Academic year 2016-2017

**Project Nº 5**

**Title:** Inmuno-Oncology in Brain Cancer: Study of a dual mechanism of inhibition of immune response associated to both CD8/PD-1/PDL1 and anti-inflammatory M2 macrophage in glioblastoma.

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**Summary**

Background: Glioblastomas (GB) possess several relevant mechanisms of immune escape. The clinical antineoplastic effect of a novel class of immune modulatory agents depends on both the expression and the interaction of these immune mechanisms. It is believed that there are two opposite subtypes of intratumoral microglia/macrophage infiltration (M2 and M1 macrophages) that suppress or activate immune response respectively. Another relevant immunosuppressive factor is PD-L1 with its corresponding T cell receptor (PD1). There are currently few published studies concerning the role of immune modulation in GB.

Goals**:** Our proposal is that a dual mechanism of inhibition of immune response exists associated to both CD8/PD-1/PDL1 and anti-inflammatory M2 macrophage effect in GB, which are expressed intensely in a subgroup of GB. We have demomstarted that the high expression of PD1/PD-L1 inhibition mechanism correlates with a poorer overall survival in GB. Moreover, we have showed that the high expression of M2 mcrophages correlates with a poorer overall survival in GB. As M1 macrophages expression correlates also with a worse prognosis, it is proposed that this supposed M1 phenotype really behaves as an immunosuppressive macrophage in GB. The immune repsonse will be considered according the molecular subtype of GB.

Methodology: A large series of clinically and well characterized GB will be studied. A complete immunohistochemical study against CD163 (M2 macrophage), CD16 (M1 macrophage), CD8, PD1 and PDL-1, and others relevant markers, will be obtained. Co-immunohistochemical study by confocal mycroscopy will be obtained. A correlation between the immune data and molecular characteristics of the GB will be carried out. A semi-quantitative assessment of the intratumoral cell density by image analysis will be performed. A complete statistical study including multivariate analysis will be

performed.

**References**

Komohara Y et al. Tumor-associated macrophages: Potential therapeutic targets for anti-cancer therapy. Adv Drug Deliv Rev 2016 Apr 1;99(Pt B):180-5.

Preusser M et al. Prospects of immune checkpoint modulators in the treatment of glioblastoma. Nat Rev Neurol 2015 Sep;11(9):504-14.

Wintterle S et al. Tumor-infiltrating lymphocytes in glioblastoma are associated with specific genomic alterations and related to transcriptional class. Cancer Res 2003 Nov 1;63(21):7462-7.

**POSSIBILITY OF PhD**

YES

* (PhD grant required)