PhD MAbImprove 2015

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Title: **Strengthening immunomodulatory effects of an anti-tumor monoclonal antibody trough combined therapies**.

Abstract: Research programs developed in our team aim at a better understanding of the relationship between cancer cells and the immune system, with the desire to understand how immune cells contribute to monoclonal antibody (Mab)-based immunotherapies.
Using the B16F10 melanoma mouse model, we showed that the TA99 Mab (an antibody directed against the TYRP1 antigen overexpressed on tumor melanocytes), significantly delays tumor development and increases mice survival, but does not allow long-term control of tumor progression. Tumor immune microenvironment analysis during the escape phase revealed a significant increase of $CD4^+$ and $CD8^+$ effector T cells, in TA99 treated mice compared to untreated group, indicating an immunomodulatory effect of the TA99 Mab. However these T cells strongly express the immune inhibitory receptors Tim3, PD1 and co-express the ectonucleotidases CD39 and CD73 responsible for adenosine synthesis, a highly immunosuppressive molecule. We also observed a strong infiltration of regulatory T lymphocytes co-expressing the same molecules. Base on these preliminary results our goal is now to better characterize immunosuppressive mechanisms developed by the tumor to counteract the anti-tumoral immune response induced by TA99 treatment. We will use the B16F10 melanoma mouse model to bring the proof of concept that therapeutic strategies combining blockade of immunosuppressive pathways together with tumor antigen targeting Mabs, could sustained immunomodulatory functions of a tumor targeting Mab such as the TA99, and allowed the establishment of a long-term anti-tumor immune response.
The specific objectives of the thesis project will be:

- **To determine immunosuppressive mechanisms responsible for tumor escape observed in TA99-treated mice**. At different time points the phenotype of lymphoid and myeloid tumor infiltrates will be analyzed, with a special focus on the influence of the TA99 treatment on the expression of immunosuppressive molecules (which immunosuppressive molecules/pathways and which timing). Then, the functional impact of these molecules and whether their expression is associated with the exhausted phenotype of T lymphocytes will be analyzed.
- **To design a strategy based on combined therapies in order to potentiate TA99 Mab immunomodulatory effects**. Following the identification of the immunosuppressive molecules/pathways associated with tumor escape to TA99 treatment, we will study both *in vivo* and *ex-vivo* the impact of blocking these inhibitory pathways together with TA99 treatment on tumor progression, mice survival and the establishment of a tumor specific and long-term protective memory immune response.
- **To study the cellular and molecular mechanisms involved in the TA99 Mab immunomodulatory effects**. We will focus on the role of antigen presenting cells recruited to the tumor microenvironment in the establishment of the anti-tumor immune response. We will compare the impact of combined therapies on infiltrated macrophages and dendritic cells phenotype *in vivo*, and study their cytokine profile and their maturation and stimulation capacities *in vitro*.