Immunotherapy based on mAbs targeting cancer cells is now developed as a valid approach to treat cancer. Suppressive mechanisms in immune responses normally play a critical role in maintaining immune homeostasis. However, these suppressive mechanisms are also considered as one of the main reasons for the failure of cancer immunotherapies because they induce peripheral tolerance of specific tumor-immune responses and allow tumor growth. Combination therapy concurrently targeting PD-1 and CTLA-4 immune checkpoints leads to remarkable antitumor effects [4].

A comprehensive panel of tools was constructed and validated aimed at evaluating the modulation of the immune system by new therapies. In immunocompetent mice, immune cells were studied for the detection of their cell markers using FACS phenotyping. We report on a panel of syngenic tumor models (4T1, A20, AB12, B16-F10, 1325, C1498, C26, C-51, CT26, EMT6, Hepa1-6, L1210, LLC, MBT-2, MPC-11, P388, Renca and TC-1) our capacity to correlate subpopulation of immune infiltrating cells and the therapeutic effects of antibodies used for FACS analyses were CD45, CD3 and CD8 for T Cell lymphocytes, were CD45, CD11b, Ly6G, Ly6C, F4/80 for macrophages M-MDSC and G-MDSC in EMT6 tumors.

Material and Methods

Immunocompetent mice were obtained from Charles River (France). Animals were orthotopically or subcutaneously injected with syngenic cancer cell lines on D0. The animals received repeated injections of antibodies directed against CTLA-4, PD-1 and PDL-1. Isoflurane was used to anaesthetize the animals before cells injection, IV treatments and termination. All logistical parameters of the study (dosing, cellinjections, raw data, lethality, behavior and routine autopsies...) were managed using Viro Manager software (Biosytems, Dijon). During the course of the experiment, animals were terminated under anesthesia when they displayed significant signs of physiological changes. Animal housing and experimental procedures were realized according to the French and European Regulations and NRC Guide for the Care and Use of Laboratory Animals. Animal facility is authorized by the French authorities (Agreement N° A21231011EA). All procedures using animals were submitted to the Animal Care and Use Committee of Oncodesign (Agreement n° 2010/63 CEE n° 2010). Tumor volume (mm3) increase was observed for responding mice treated with PD-1 or CTLA-4 mAbs.

Conclusions and perspectives

Novel therapeutic strategies are being developed that aim to implicate the immune system in the initiation, development and progression of tumors, by blocking or redirecting the immune effectors against cancers.

Pending new generation of humanized mouse models, the growing interest in immunology as a cancer therapy shows the limitation of xenograft models in immunocompetent animals. A more effective approach is the use of syngenic mouse models.

We report on a panel of syngenic tumor models our capacity to correlate subpopulation of immune infiltrating cells and the therapeutic effects of new antibodies generation directed against CTLA-4, PD-1 and PDL-1 antigens.