The idea that the immune system can be harnessed to destroy tumors has been pursued for over a century. For many years extensive efforts were put in the development of cancer immunotherapy, i.e. therapeutic approaches aimed at boosting the intrinsic immune mechanisms to eliminate cancer cells. The major concept was based on the hypothesis that the immune system of cancer patients lack sufficient power to mount an effective antitumor immune response. Therefore, the major strategies were focused on finding immunostimulatory pathways that included recombinant cytokines, immune adjuvants or nonspecific stimulators isolated from infections microorganisms. Despite some minor successes, the approaches turned out to be essentially limited by toxicities. Experimental studies in animal models have made it clear that the immune system can easily recognize tumor-associated antigens, but remains quiescent. Several potential mechanisms responsible for this insufficiency have been identified and revealed that the interference with pathways dampening immune reactivity appears to be more effective in cancer patients than over-stimulation of effector mechanisms of lymphocytes. An important inflection point in cancer treatment was reached with the approval of the so called immune check-point inhibitors, which are antibodies targeting CTLA-4, PD-1 or PD-L1 molecules. Like never before the medical community is witnessing durable responses in cancer patients that occur even in those tumors that were considered to be non-immunogenic. Spectacular therapeutic efficacy exceeds even recent expectations making cancer immunotherapy a routine therapeutic option for clinical oncologists. However, complete antitumor responses are limited to only a minority (20-30%) of patients. Therefore, identification of molecular mechanisms involved in the resistance to cancer immunotherapy is of utmost importance. Previous studies and our preliminary findings reveal that one potential mechanism involved in the interference with anti-tumor immune effector mechanism might involve the activity of arginase-1, an enzyme that degrades L-arginine in the tumor microenvironment. In the absence of L-arginine T lymphocytes cannot be activated due to decreased levels of components of the antigen recognition system. Therefore, using both genetically engineered tumor models as well as antibodies against check-point molecules we plan to determine whether arginase-1 is a potentially druggable target for the combination immunotherapy. This knowledge is necessary to better understand molecular mechanisms involved in the development of tumor-associated immune response. The results of this project might also be helpful in identifying novel targets for cancer treatment, better understanding of the shortcomings and adverse effects observed in cancer patients undergoing cancer immunotherapies and in finding novel areas to be exploited in the fields of immunology and experimental oncology. Even if the role of arginase-1 would turn out to be important only in a subgroup of patients, the results of this project might be of great clinical importance.