The main goal of proposed project is to understand how cancer cells are capable of shaping tumor microenvironment (TME), in order to escape from immune surveillance. We recently discovered a metabolite, that accumulates at supra-physiological concentrations in the TME and is capable of inhibiting the cytotoxic activity of immune effector cells toward target cancer cells. This is a strong indication that this metabolite renders TME more suppressive toward infiltrating lymphocytes, so it evolves to a very hostile environment to immune cells, and eventually cause resistance to immunotherapeutics. This project aims at investigating the molecular mechanisms activated by this metabolite and the changes, that are induced in both cancer and immune cells. We will also analyze the effect of metabolite on the expression of activating and inhibitory receptors on the surface of immune effector cells. Using pharmacological modulators of metabolism we plan to exploit few avenues to reduce production of the metabolite by cancer cells, and enhance its clearance from TME. Using mouse models of tumor growth, we will study the effects of metabolism modulators on the intensity of tumor infiltration by lymphocytes involved in cancer cell recognition and killing. Lastly, we will assess the efficacy of immune checkpoints inhibitors, prior and after deactivation of the metabolite-mediated pathways. The knowledge gained during the implementation of this project will help in confirming the role of particular metabolite in inhibiting the anti-tumor immune response and suggest strategies targeting this metabolite, to ensure better host immune response against the tumor, and enhanced efficacy of immune checkpoint inhibitors, when applied.