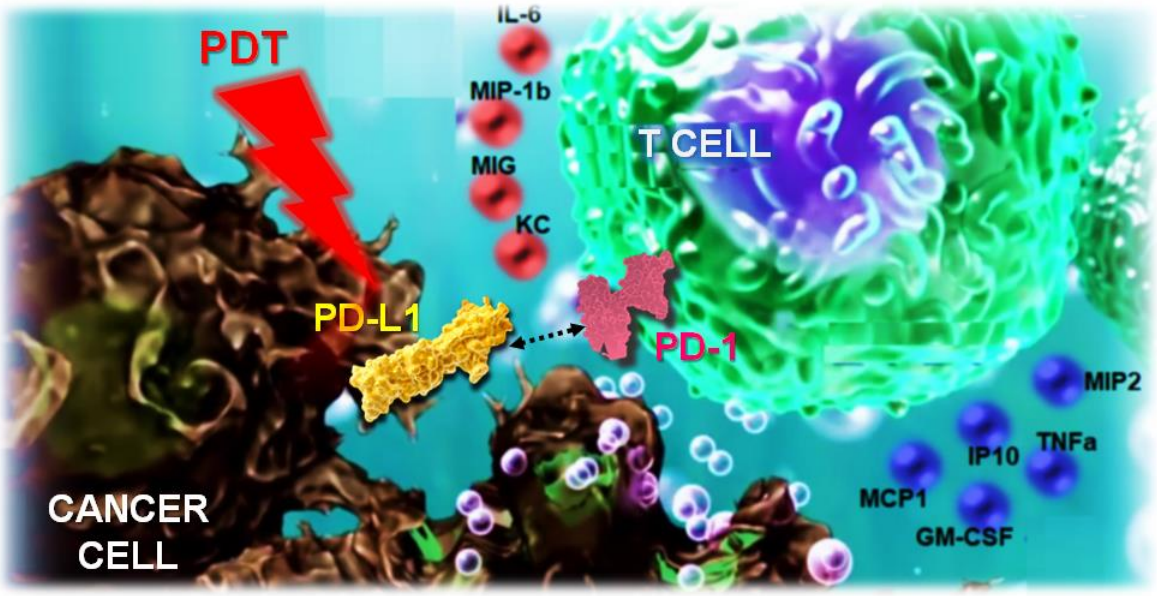
Photodynamic therapy combined with PD-1/PD-L1 blockade immunotherapy: new possibilities for the treatment of immunogenic cancers

Cancer is the second most common cause of death in the world. It is a pathological condition, in which the homeostasis is disturbed in terms of proliferation, apoptosis, cell differentiation and functioning of repair systems. Moreover, the features of the cancer that limit the effectiveness of current treatment regimens include: i) ability to stimulate angiogenesis; ii) ability to infiltrate surrounding tissues and create distant metastases; iii) ability to escape from the control of the immune system, which under normal conditions prevents tumor progression. In recent years, the negative immune checkpoints inhibition has become an attractive strategy for cancer treatment. The most common way is the blockade of binding between the programmed death 1 receptor (PD-1) and its ligand PD-L1. However, in order to achieve total therapeutic success, it is crucial to apply a strategy operating in a multiple directions, through various biological mechanisms aimed at complete destruction of the tumor. An example of multimodal therapy is photodynamic therapy (PDT). PDT involves the application of a compound that, when activated by light at the target site, results in the generation of reactive oxygen species (ROS) that lead to the cancer cells death, closure of blood vessels and stimulation of the immune system.



Scheme illustrating the possibility of combining PDT with immunotherapy

The aim of this project is to develop effective anticancer therapy protocols combining PDT with PD-1/PD-L1 immune checkpoint blockage. Within the framework of the research tasks envisaged in the project, it is planned to obtain and characterize photosensitizers targeting the tumor microenvironment (TME) and to determine the photochemical mechanisms which they undergo after being excited by near infrared radiation (NIR). The next stage of the study will be to test the cytotoxicity and phototoxicity of these photosensitizers, first against cells with different levels of PD-1/PD-L1 expression, and then in 3D cell cultures, 3D vessel networks and organoids. Pharmacokinetic and toxicological studies on selected animal models and monitoring of tumor hypoxia are also expected to optimize and improve the effectiveness of therapy. The key step of the study will be to assess systemic anticancer immunity induced by PDT combined with immune checkpoints blockade (PD-1/PD-L1).

We postulate that photodynamic therapy combined with immunotherapy against PD-1/PD-L1 may prove to be an effective approach in the treatment of tumors resistant to other modalities. The combination of PDT with immunotherapy proposed in the project will certainly contribute to strengthening the anticancer immune response in order to not only destroy primary tumors but also to control distant metastases.