DESCRIPTION FOR THE GENERAL PUBLIC

The main purpose of the project is the development of chemoimmunotherapy based on immunomodulatory dose of MTX-HES nanoconjugates supported by immunotherapy consisting of vaccines containing dendritic cells stimulated with tumor antigens and genetically modified to silence the expression of IL-10 receptor.

These nanoconjugates are a new type of therapeutic compounds that resulted from merger of drugs certified and currently widely used in the medical treatment – methotrexate used both in antitumor therapy, and for the treatment of autoimmune diseases and hydroxyethyl starch, which is amylopectin polymer already used in medicine (as colloidal plasma volume expanders). Conjugation of MTX with HES extends the life of MTX in the body and reduces side effects compared to MTX administered in free form. MTX-HES nanoconjugates exhibits an antitumor activity and their use in antitumor therapy is the subject of patent application.

A thorough understanding of the interaction, between tumor cells and immune cells, should enable us the conscious use of the particular elements of immune system for the fight against cancer. However, current attempts using immunotherapy are primarily focused on the induction of specific anti-tumor responses while only the complex treatment can influence on the tumor microenvironment effectively. Hence, immunotherapy becomes the more frequently employed method for cancer treatment used to enhance the conventional chemotherapy, while dendritic cells (DCs) are one of the most promising strategies to induce antitumor immune responses, since the DCs are professional antigen presenting cells. Their main function is to process antigen material and present it on the cell surface to the T cells of the immune system to T cells, which is important in the generation of antitumor immunity. Moreover, the employment of the DC-based immunotherapy can be a way to reduce side effects of cytostatics enabling the shortness of the administration regimen or decrease of the drug doses.

In the environment of developing tumor there are immunosuppressor factors responsible for inhibitition of the immune response, and therefore in this project immunotherapy will be used for improving anti-tumor effect of chemotherapy.

Dendritic cells express the interleukin-10 receptor (IL-10R) on their surface. Dendritic cells responding to IL-10 abundance in tumor environment DCs can acquire regulatory properties, and through producing higher amounts of IL-10 they may promote the generation of T regulator cells and induction of effector T cells anergy. Therefore, chemoimmunotherapy based on the application of MTX-HES will be supported by immunotherapy including DC-based vaccines stimulated with tumor antigens and silenced IL-10R expression. The receptor down-regulation reduces sensitivity of DCs to IL-10 present in the tumor microenvironment and contributes to targeting and enhancement the antitumor immunity.

This will contribute to develop a new strategy of chemoimmunotherapy consisting of these nanoconjugates combined with cellular vaccines based on dendritic cells with silenced expression of IL-10R and stimulated with tumor antigens (BM-DC/shIL-10R/TAg). We expect that this treatment will result in full reactivation of the host immune system and induction of potent and specific antitumor responses in mouse MC38 colon carcinoma model.

This project is a connection between our earlier research. On the one side is a continuation of studies where nanoconjugates of methotrexate and high molecular polysaccharide carriers are used in anticancer therapy, but on the other, it is also continuation of research, which are focused on application of DC-based vaccines during the treatment of MC38 colon carcinoma-bearing mice.