

"Ovarian cancer" is a collective term for cancers that differ significantly in their response to treatment. The most malignant gynecological cancer remains high-grade serous ovarian cancer (HG-SOC). Ovarian cancer causes over one hundred thousand deaths per year. Early screening and detection methods are ineffective.

Treatment includes surgery and chemotherapy with cytostatics, i.e. drugs that are toxic to cancer cells (e.g. cisplatin or carboplatin in combination with paclitaxel). However, 80% of patients develop resistance to treatment and almost all patients die due to relapse. Although new therapeutic approaches include targeted therapies (e.g. monoclonal antibodies), the results to date show that they extend progression-free survival, but not overall survival. The lack of effective diagnostics resulting in late diagnosis and five-year survival statistics mean that other innovative treatment methods are urgently sought.

Patients with advanced ovarian cancer often develop ascites, i.e. abnormal fluid accumulation in the abdominal cavity. The cellular components of the ascites microenvironment include spheroids, T cells, tumor-associated macrophages and cancer-associated fibroblasts, and myeloid-derived suppressor cells. Ascites facilitate the spread of tumor cells in the peritoneum, creating lethal metastatic lesions. This makes the control of ascites a major target for new therapies.

Among the most modern potential therapeutic tools in oncology are oncolytic viruses. They are able to selectively replicate in tumor cells, causing the gradual destruction of pathological foci. Oncolytic viruses can be genetically modified in various ways, e.g. to stimulate the host's immune response against the tumor, to deliver specific therapeutic substances to tumor cells, to enable the induction of tumor cell apoptosis or reducing the so-called desmoplasia accompanying some tumors.

The aim of the simple Project is to test the usefulness of the combined action of genetically modified oncolytic myxoma virus constructs in experimental therapy of ovarian cancer in combination with a cytotoxic fusion protein. The fusion protein, IL-13-DT390 consists of the cytokine IL-13 and a fragment of diphtheria toxin (DT390). This protein should be highly effective and selective in eliminating cancer cells showing overexpression of the IL-13R α 2 receptor for which IL-13 is a ligand. Such overexpression, present on ovarian cancer cells, makes the fusion protein IL-13-DT390 a promising drug candidate. The project aims to achieve its goal by examining the effectiveness of destroying ovarian cancer cells at two levels. The first is research in vitro conditions, i.e. in two-dimensional culture as well as in three-dimensional (3D) culture, the so-called. spheroids, which allows for the reproduction of the interactions of cultured cells with the extracellular matrix. The second level is in vivo research and is to consist of therapy trials using two models of ovarian cancer induced experimentally in mice.

We plan to study ovarian cancer spheroids after their isolation directly from ascites samples of patients in an advanced stage of the disease or by deriving them from ovarian cancer cell line cultures. The data obtained so far indicate that myxoma virus constructs are indeed capable of infecting and eliminating cancer cells present in spheroids isolated from ascites. This result makes it particularly worthy of closer examination, firstly due to the relatively easy experimental approach, and secondly due to the intuitively obvious translation into clinical application. The reasons for undertaking the discussed research topic are the low effectiveness of the current treatment of ovarian cancer and the socio-economic attractiveness of the proposed approach. The most important expected effects of the Project is the progress in eliminating cancer cells present in spheroids isolated from ascites obtained from patients with advanced ovarian cancer and success of experimental anticancer therapy of ovarian cancer in a preclinical animal model. The significance of this multidisciplinary Project which combines knowledge from the fields of biology, oncology, virology, drug design chemistry and mouse models of cancers, is the study of a new relatively simple and relatively inexpensive approach to experimental therapy of advanced ovarian cancer. Given the failures of ovarian cancer treatment and the large financial outlays on the therapy of this disease, the results confirming the potential assumptions of the Project may have a significant impact on the development of personalized treatment therapies or for extending the survival of patients.