Ovarian cancer is the leading cause of death from gynecological cancers. In this project, we will focus on one of the most important and still underinvestigated problems in ovarian cancer pathophysiology, that is, the mechanism of disease recurrence. The term recurrence (or relapse) means that the disease returns a second time after a patient with primary disease has been successfully treated. There are some theories regarding why cancer recurs, and the most common theory states that the secondary disease is caused by a few of the original cancer cells that survived the initial treatment. Sometimes, these cancer cells survive because they are disseminated to other parts of the body and are too small to be detected during the follow-up assessment immediately after treatment. There are also suggestions that relapse may be associated with the presence of so-called cancer stem cells and/or the presence and further reactivation of dormant cells. The latter term refers to a fraction of cancer cells that have temporarily lost the ability to proliferate, but under a permissive tissue environment, may start to grow and form tumors again.

Surgery (debulking/cytoreduction) is the main treatment for ovarian cancer patients. According to the current guidelines, optimal debulking surgery is aimed at leaving no visible cancer or at reducing the tumor size to less than 1 cm in maximum diameter. However, when primary debulking is suboptimal or when the risk of gross residual disease is high, the patients are subjected to chemotherapy, in which platins and taxanes (carboplatin + paclitaxel) are used as the gold standard treatment. Unfortunately, despite well-established standards of treatment, approximately 70% of ovarian cancer patients relapse within 2 years of primary cytoreduction and first-line chemotherapy. Although various scenarios have been developed to treat relapsed disease, such as secondary cytoreduction or second-line chemotherapy, the prognosis is usually poor.

In this project, we intend to investigate the mechanism of ovarian cancer relapse based on the awakening of dormant cancer cells. Specifically, we propose a hypothesis suggesting that dormant cancer cells are awakened by normal cells of peritoneal origin (mesothelial cells and fibroblasts) that senesce prematurely in response to exposure to carboplatin and paclitaxel. This prediction is based on previous observations that platins and taxanes may induce senescence in other cell types, which has been the cause of the development of various chemotherapy-induced side effects. Importantly, we hypothesize that signals derived from senescent peritoneal cells are transmitted to dormant cancer cells via exosomes. Exosomes are very small (~30-150/200 nm) extracellular vesicles released from a cell by a process called exocytosis. Recently, strong evidence has indicated that exosomes play important roles in cancer progression. Moreover, exosome constituents may be critical for a significant portion of the cancer-promoting activity of senescent cells.

In this project, we propose a completely new approach to ovarian cancer recurrence. If our hypothesis is found to be correct, then the results will have indicated that dormant cell awakening may constitute an unexpected, iatrogenic (therapy-related) side effect of first-line chemotherapy. This outcome will, in turn, create an urgent need to redefine outcomes (the pros and cons for a patient) of classic ovarian cancer chemotherapy. Moreover, the project will shed new light on drug-induced senescence of normal cells as the potential culprit of disease relapse. The identification of the involvement of senescent cell-derived exosomes as messengers of dormancy termination will help with gaining a better understanding of the molecular background of this process.