Epithelial ovarian cancer (EOC) characterizes the highest mortality rate among gynecological tumors. 75% of patients are diagnosed at advanced stages due to an asymptomatic course and 75% of these patients die within 5 years. The causes of such a high rate of mortality seem to be related to the complex biology, huge heterogeneity of tumors and immunosuppression in tumor immune microenvironment (TIME). In the TIME, the principal "mission" of immune cells is to execute an antitumor program, but a portion of such cells becomes a confederate of the tumor. Taking the above into consideration, myeloid-derived suppressor cells (MDSCs) can play a pivotal role as they are co-responsible for the inhibition of the immune system.

MDSCs represent a heterogeneous population of immature myeloid cells (IMCs) which include dendritic cells, macrophages, and granulocytes in various stages of differentiation. There are three major subpopulations of MDSCs - monocytic (M)-MDSCs, polymorphonuclear (PMN)-MDSCs and early-stage eMDSCs. Although a variety of key surface markers MDSCs have been described, and researchers established immunophenotype criteria for these cells, their profile appears to vary in different cancers and even between patients. Besides, research indicates that the percentage of MDSCs can be significantly increased in patients with cancer and reveals its important roles in tumor growth, metastasis and as a negative prognostic factor in cancer.

To our knowledge, until date, the multiparametric profiling of cMDSCs on different molecular levels (genes, miRNAs, proteins) has not been described. Based on prior reports concerning the immunosuppressive function of cMDSCs in different types of tumors, immunosuppressive tumor immune microenvironment (TIME) in EOC together with the prognostic significance of cMDSCs, we hypothesized that abnormal multi-omics molecular signature of cMDSCs may be crucial in the biology of EOC. Therefore, in this project we proposed multi-omics molecular profiling of cMDSCs in EOC.

In the first step, we will focus on screening studies of a putative cMDSCs-related molecular factors on transcriptomic (RNA; RT^2 Profiler PCR arrays), epigenomic (miRNAs; miScript miRNA PCR arrays) levels in the peripheral blood of EOC patients. In parallel, protein arrays will be used to screen for cytokines present in human plasma and cell culture supernatants (proteomic level). Such approach will allow us to identify the direction for further studies dedicated to the cMDSCs-specific molecular pattern in cancer patients.

In the second step, we will focus on validation of putative cMDSCs-related molecular signatures. In this case the droplet digital PCR (ddPCR) will be done to validate for gene and miRNAs expression changes in the study groups. In parallel, protein expression analysis (multiparametric flow cytometry) will be done on patients' peripheral blood mononuclear cells (PBMCs) to validate protein in the three different cMDSC subsets (i.e. M-, PMN-, eMDSCs). Moreover, Bio-plex assay will be performed for validation of cMDSCs-related cytokines in the plasma and cell culture supernatants.

Multiparametric analysis can indicate a set of molecular factors which can be used as "identity cards" for MDSCs in EOC. By determining the transcriptomic, epigenomic, proteomic states of such cells in parallel, it may be possible to select the specific targets for the future therapy. The manipulation/modification of MDSCs on the different multi-omic levels might offer an effective "weapon" to reverse unfavorable changes in MDSCs which may be of clinical benefit, without the global effect on other immune cells resulting, as a side effect, in general immunosuppression.