

**Research project objectives/Research hypothesis:** Head and neck squamous cell carcinomas (HNSCC) are a group of carcinomas which affect the oral cavity, the pharynx and the larynx. They represent more than 90% of all malignant tumors in the head and neck region. In 2012, more than 600,000 cases have been registered worldwide, leading to HNSCC being the seventh most common malignant tumor disease. Despite an intensive study of the carcinogenesis of HNSCC and the development of new therapeutic concepts, the average 5-year survival rate has remained less than 50% for decades. Thus, there is an urgent need for identification of new biomarkers and therapeutic targets for treating HNSCC. For the growth of solid tumors such as HNSCC, an adequate autonomous blood supply is essential. Tumor angiogenesis is based mechanisms include the classical capillary sprouting, the recruitment of endothelial progenitor cells from the bone marrow and the division of blood vessels. In addition, tumors are able to increase their blood supply by using tumor cells to migrate into the proximity of existing vascular structures, mimicking endothelial cells (ECs), or differentiating themselves into ECs. A novel attempt to explain the molecular and genetic changes which originate from tumor cells and which affect the surrounding tissues and the host immune system has recently focused on extracellular vesicles (EVs) with a diameter of 30-150 nm also known as “exosomes”. They are produced by all cells, but tumor cells are especially active tumor-derived exosome (TEX) producers. Exosomes carry a variety of signaling molecules on their surface membrane and in their lumen are DNA, mRNA and microRNA (miR), enzymes, growth factors etc. The TEX play an important role in the suppression of the immune system in tumor microenvironment (TME) and in periphery, which therefore promotes tumor progression. Furthermore, their effects on blood vessel development and on the process of angiogenesis are great current interest. Based on our preliminary results and literature data, **we hypothesize** that TEX influence the proliferation of endothelial cells (ECs) and angiogenesis in TME. Therefore, **the aim of the current project** is to investigate the role TEX in angiogenesis and tumor progression in HNSCC and to investigate the mechanisms underlying this process using *in vitro*, *in vivo* and *ex vivo* models.

**Research project methodology:**

Our project involves the use of a panel of the state-of-the-art techniques, such as molecular biology techniques, functional cell assays, flow cytometry, immunohistochemistry, confocal microscopy, *in vivo* imaging. An important aspect of the design of this project is the systemic approach, since we will investigate the role of TEX not only in *in vitro* and *ex vivo* models, but in addition will use a orthotopic mouse model of HNSCC as a crucial step for interrogating a true involvement of studied pathways in tumor progression and angiogenesis.

**Expected impact of the research project on the development of science:**

Our project will delineate a novel mechanism used by HNSCC in tumor progression and angiogenesis. The knowledge gained on the angiogenic role of TEX can be further directly used in the future research on tumor evasion, but also will undoubtedly be useful for understanding similar processes, occurring both in pathology and under normal conditions. In our project, we delve into how the studied TEX can be potentially exploited therapeutically to improve treatment regimens and to improve outcomes for HNSCC patients. The proposed project is unique and presents original approach to the search of role of TEX in HNSCC. The project will be realized in collaboration with a group of immunologists from the University of Pittsburgh Cancer Institute (UPCI), Pittsburgh (USA), headed by Prof. Theresa L. Whiteside. The project we will strengthen the co-operation between the leading Polish and foreign research centers in the area of study, and contribute to the further dynamic development of Polish science, as well as the broadening of the general knowledge in the field of experimental oncology and immunology.