Head and neck squamous cell carcinoma (HNSCC) is a biologically diverse and genetically heterogeneous disease. It accounts for more than 650,000 new cases annually and more than 350,000 deaths. The classical major risk factors of HNSCC occurrence are tobacco and alcohol consumption, and in the past few decades, human papillomavirus (HPV) has emerged as a novel risk factor for these cancers, defining a new subtype of tumor. It has been shown that HPV-positive (HPV+) HNSCC is more sensitive to treatment and is characterized by better survival. The overall survival for 3-year follow-up is estimated for 82% of HPV+ and 57% for HPV- HNSCC. HPV status of cancer cells defines their biological behavior which may lead to variable sensitivity to anticancer therapies. **We are currently noting high mortality of HNSCC patients, an increased number of HPV cases, and still lack the efficient, personalized, HPV status dependent treatment.** Therefore, the search for new disease biomarkers and therapeutic targets is currently one of the most important fields of molecular medicine.

Cancer is a consequence of accumulative genetic mutations in concert with epigenetic alterations, as well as environmental factors. Distinct from genetic mutation, epigenetic influences refer to modifying gene expression without permanent changes in the genomic sequence. They are preferentially applied in cancer cells due to its reversible and faster regulation compared to genomic evolution. Epigenetic drugs (epidrugs) are a group of promising target therapies for cancer treatment acting as coadjuvants to reverse drug resistance in cancer. Nowadays clinical trials focused on evaluating the effect of these epidrugs alone or in combination with other anticancer therapies. The use of epidrugs promises to be an effective tool for reversing drug resistance in some patients with cancer. Recent studies demonstrated that, in many types of cancers various oncogenic signaling pathways are modulated by the RNA methylation- epigenetic modification occurring in 6th position of adenosine (m^6A). RNA methylation participates in the occurrence and development of tumors by affecting splicing, nucleation, stability, and immunogenicity of RNA. RNA methylation affects tumor immunity through the maturation and response function of immune cells**.** However, there is lack of data concerning RNA methylation, HPV-status, and treatment response in HNSCC at once that makes this project highly innovative. Thus, **this application aims to determine the epigenetic signatures based on RNA methylation that differentiate both HPV+ and HPV- driven HNSCC and characterized novel epidrugs for therapy improvement.**

The main goal of the project will be achieved through the following specific objectives:

1. Identifiaction of differenial mRNA m^6A sites and expressed genes in HPV+ and HPV- HNSCC
2. Mechanistic studies on specific binding of methylated mRNA to m^6A RNA regulators-searching of epidrugs
3. *In vitro* validation of epidrugs outcome on HNSC HPV+/- cell lines and primary HNSCC cells
4. *In vivo* validation of the effects of epidrugs in a mouse model

We assume, that by execution of presented experiments, we will be able to identify and validate the new m^6A methylation dependent epidrugs for the standard treatment improvement and personalization of HPV status dependent HNSCC patients.