DESCRIPTION FOR THE GENERAL PUBLIC

DNA helicases are ATP-dependent enzymes often referred to as “the guardians” of the genome. They have been shown to play fundamental functions in DNA replication and recombination, transcription, DNA repair and telomere maintenance. Thus, they are responsible for genome stability and integrity. As DNA helicases are frequently deregulated in cancer, therefore, they represent new, potential therapeutic targets. Literature data have shown that mutations in helicase encoding genes predispose patients to develop cancer and may modulate patient responses to radio- and chemotherapy which are processes based on induction of DNA damage and cell death. However, the exact mechanisms and the roles of these aberrations in cancerogenesis remain unknown. Since conventional anti-cancer therapy (radio- and chemotherapy) is generally aimed to inhibit cancer cells by induction of DNA damage, the sensitivity of tumor cells to the treatment partially depends on their ability to repair DNA. Therefore, DNA repair involved genes are crucial for further studies in relation to cancerogenesis.

Gliomas are the most common brain tumors, amongst which glioblastoma (GBM) is the most malignant, highly resistant to current treatment strategies. Despite significant advances in oncological therapy in recent years, clinical prognoses for GBM patients remain poor and mean patient survival is 15 months. Therefore, there is an urgent need for an effective targeted therapy for human glioma based on newly identified molecular targets.

The main goal of the project is to verify hypothesis, based on our preliminary results and available literature data, that mutations in one of RecQ helicases family play an important role in pathogenesis of human gliomas and their response to chemotherapeutics. In order to achieve our aims we will take advantage of clinical tissue samples of low- and high-grade gliomas and human glioma cell cultures (*in vitro* study).

We will analyze collected human glioma specimens for the presence of mutations in the *RECQL4* gene, its frequency and localization within the gene using an innovative and effective ultra-deep sequencing method. We will evaluate the expression of helicase on mRNA and protein level in low- and high-grade glioma specimens. We will also determine a functional role of this helicase in human glioma cells by silencing of the gene using small interfering RNA (siRNA). Besides, we will evaluate effect of mutation and its localization on enzymatic (helicase) activity and resistance of glioma cells to chemotherapeutic drugs.

The project will widen our knowledge and understanding of the gene alterations underlying aberrations in mechanisms crucial for genome integrity and stability which potentially could be involved in pathogenesis of malignant gliomas. Implementation of the project may provide a new insight for future cancer targeted therapy.