DNA is a vulnerable molecule and its integrity is relentlessly threatened by innumerable cellular and environmental agents producing daily dozens thousands of lesions in each cell. Luckily, cells are equipped with a myriad of DNA repair mechanisms that counteract those lesions. Nonetheless, at times the lesion escapes the repair program or is not fixed on time. The consequences of damage persistence in genetic material could be deleterious for the cells, especially for the dividing ones, as most of the DNA lesions block the DNA duplication, a critical step in cell multiplication, which could cause cell death. This is why, for the sake of survival, cells can temporarily tolerate damage to their genetic material. One of such tolerance mechanisms employs specialized enzymes, translesion synthesis (TLS) polymerases, that can duplicate damaged DNA. TLS polymerases act, however, as a molecular double-edged sword, while permitting cell survival often, especially when replicating undamaged DNA, make mutations that could lead to a cancerous transformation of the cell. This is why the engagement of TLS polymerases needs to be under strict control.

A tight governing seems to be particularly important in the case of polymerase iota, the most mutagenic and rather puzzling human polymerase. Its precise cellular role is not fully understood, however deficiency of the enzyme was shown to sensitize cells to oxidative stress that is also a side effect of normal cellular metabolism. It has been also shown that the amount of polymerase iota is specifically induced in hypoxia conditions characteristic for solid tumor environment suggesting the participation of polymerase iota in tumorigenesis. Interestingly, tumorigenesis has been correlated both with lack and with overproduction of polymerase iota, underlining the necessity of precise correlation of this enzyme. Importantly, polymerase iota and other TLS polymerases, thanks to their ability to bypass DNA lesions, can impede anticancer therapies that are based on introducing DNA damages into rapidly dividing tumor cells. Modulating TLS polymerases is a promising method to improve cancer therapy.

Aim of the project: **To reveal the mechanism involved in the control of polymerase iota's cellular level and function.**

Our preliminary results indicate that p300 acetyltransferase has a significant influence on the regulation of polymerase iota.

Planned research: In the proposed project we will explore the p300 influence on the regulation of polymerase iota abundance on different levels. We will also investigate the relations between polymerase iota and p300 in hypoxic conditions. In the proposed research we will utilize a whole range of biochemical, microscopic, bioinformatics, and molecular methods.

Expected outcomes: Besides discovering the mechanisms of polymerase iota protein level control and polymerase iota functioning, we expect our research to additionally provide some inputs into the regulation of p300-dependent mechanisms implicated in numerous cellular processes. Additionally, in a long run, we expect the result of our research to be useful in designing new, more focused, personalized cancer therapies.