Tens of thousands DNA lesions, induced by environmental factors or as a consequence of normal metabolic processes, occur every day in each human cell. Most of those DNA lesions are recognized and repaired by one of the multiple DNA repair mechanisms that our cells are equipped with. However, none of the processes are 100% efficient and consequently some of the DNA lesions escape the repair route. The consequences of damage presence 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 temporal acceptance of the lesion in the cell is beneficial, as it allows the cell to survive and later repair the lesion. One of such DNA damage tolerance mechanisms is translesion synthesis (TLS) that employs special types of enzymes able to bypass the lesion. Such processes however, does not go by without any consequences and often TLS polymerases, enzymes proficient on damaged DNA, introduce a lot of mutations on an undamaged template, which could cause cancerous transformation of the cell. This is why TLS polymerases need to be under strict control to permit the lesion bypass, but inhibit further mutagenic synthesis. Cells can control presence and the role of proteins in many ways and it looks that activity of TLS proteins is often regulated by so called posttranslational modifications of their molecules. Mostly it takes place by introducing new functional groups, or even small regulatory proteins such as ubiquitin to some of their lysine residues.

The goal of the proposed project is to characterize how posttranslational modifications influence the cellular role of polymerase iota.

Polymerase iota is the most mutagenic of human polymerases. Its precise cellular role is still not fully understood, however lack of polymerase iota have been associated with sensitizing cells to oxidative stress that is also side effect of normal metabolism. It was also shown that the lack of this polymerase activity causes an increase in mesynchymal tumor frequency. Additionally, deregulation of polymerase iota has been shown for various types of cancer. What is more, polymerase iota and other TLS polymerases, thanks to its ability to bypass variety of DNA lesions, can counteract many of anticancer therapies based on introducing DNA damage in actively dividing tumor cells. So it is extremely important to identify mechanisms engaging TLS enzymes to design new, more focused and personalized cancer therapies.