Tuberculosis (TB) is an infectious disease caused by one of the most dangerous bacterial pathogens known to human kind, *Mycobacterium tuberculosis* (*Mtb*). Latest estimates reveal that each year TB kills about 1,5 million people worldwide. There had been 9,6 million new incidents of TB in 2014 year and approximately 1/4 of the global human population is infected with *Mtb*. Most of infected individuals have dormant (latent) TB and will remain symptomless throughout their lifetime but approximately 5% of them will develop the active form of tuberculosis at some point in their life. Importantly, there is growing incidence of tuberculosis cases caused by drug- and multi-drug resistant (DR and MDR) strains, the spread of which is a serious threat to the public health. Anti-tuberculosis therapy is complex, time- and resource-consuming and requires use of several drugs at the same time for prolonged periods of time. Many of currently administered antituberculosis drugs have multiple harmful side effects. Tuberculosis is an airborn disease, which spreads by cough droplets originating from an infected individual and leads to mycobacteria getting into the lungs along with the inhaled air. The innate immunity plays an extremely important role in fighting *Mtb* infection and the development of TB symptoms is largely a result of inadequate antibacterial immune response of the host. This is often connected with the weakening of the immune system, as incidence of TB increases with age, and innate as well as acquired immunodeficiencies promote TB infection development. This is why TB often coincides with AIDS, and has killed almost 450,000 HIV positive people only last year. The tubercle bacilli, during transmission and throughout infection, reside in a particularly hostile environment, rich in mutagens, which may cause damage to their genetic material. Evolutionary success of *Mtb*, as an intracellular pathogen, can be accounted to its ability to quickly and accurately accommodate to changing environmental conditions and to prevent and repair DNA damage.

Mtb involves numerous repair systems in the response to harmful agents causing DNA damage. In silico analysis of genomes from different mycobacterial species showed the presence of gene encoding proteins involved in a simple reversion of DNA damage like: repair via excision of the damaged DNA base -BER (Base excision repair), excision of the entire nucleotide -NER (Nucleotide excision repair), homologous recombination -HR, non-homologous DNA end joining -NHEJ and the SOS repair system. Surprisingly, mismatch repair system (MMR), showing high conservation in the process of evolution of species, was not identified within the *Mtb* genome, despite the uniquely high preservation of integrity observed for mycobacterial genomes. In various microorganisms, including intracellular pathogens, multiple genes associated with DNA repair have been described as essential virulence factors. Severe damage of genetic material, resulting in inhibition of DNA replication process, requires fast and well-coordinated cellular response. In most bacteria, including *Mycobacterium tuberculosis*, the SOS system, with a key role of RecA recombinase and LexA repressor, is turned on in case of this kind of events. In recent years, high throughput methods of analysis of the global gene expression (microarray, RNAseq) allowed identification of genes directly involved in the SOS response system, as well as those which are involved in the DNA repair that do not require participation of RecA protein.

The main objective of this project is to elucidate the mechanisms that govern RecA-independent SOS DNA damage repair responses in *Mycobacterium tuberculosis* (*Mtb*). The project will provide detailed description of factors participating in RecA independent SOS repair regulation. The project will also try to address and clarify involvement of the two DNA repair proteins, a RecA paralogue -RadA and DNA integrity scanning protein -DisA co-expressed with it, in the RecA independent response to DNA damage.

The characterization of investigated here DNA damage response proteins will help to evaluate their potential to become future anti-tuberculosis drug targets. Importantly, the proposed project will broaden our knowledge about the regulatory mechanisms of most relevant DNA repair pathways in bacterial cells. Since such mechanisms are often an universal and DNA damage repair processes are very well preserved throughout of the domains life, our study may lead to interdisciplinary findings. This is especially important as an erroneous or inadequate DNA repair is responsible for the process of mutagenesis, which leads to acquiring of antibiotic resistance in bacteria and development of cancer in humans. Multiple DNA repair enzymes are already being targeted for anticancer therapies, proving that better understanding of the DNA damage responses is critical for development of antimicrobial and anticancer therapies.