Growth and division are fundamental aspects of life. The blueprint for development and maintaining an organism is encoded in DNA. DNA replication, the vital process that leads to duplication of cellular genetic material, is extraordinarily complex. Although DNA replication is highly faithful, it is not entirely error-free. Flaws in DNA replication, collectively referred to as replication stress, are a key contributor to genomic instability and might become a hallmark of cancer. To prevent harmful genome rearrangements during DNA replication, cells have evolved numerous repair pathways to correct errors and fine-tune the replication process. These pathways are regulated by specialized protein modifications called post-translational modifications.

One critical post-translational modification is SUMOylation, in which a small protein called SUMO (Small Ubiquitin-like Modifier) is attached to other proteins, regulating their function and stability. SUMOylation is essential for cell survival and plays a key role in DNA repair. Disruption in SUMOylation pathway can lead to various human diseases, including several types of cancer. Although SUMO was discovered nearly 30 years ago, it still remains poorly understood, largely due to difficulties in its detection.

It was shown that SUMOylation is crucial for replication stress response. My contributions to this field include demonstrating how SUMOylation regulates the resumption of DNA synthesis during replication stress by facilitating the correct engagement of the homologous recombination repair pathway in a model organism *Schizosaccharomyces pombe*. Intriguingly, I have found that DNA repair at replication stress sites is highly organized within the three-dimensional structure of the nucleus, that is moderated by SUMOylation.

The unanswered questions central to this project aim to uncover how SUMOylation fine-tunes DNA repair in the crowded environment of eukaryotic nuclei:

- How does SUMOylation regulate the repair factors to efficiently restart altered DNA replication?
- How does the composition of SUMO-modified proteins vary depending on nuclear localization of replication stress site?
- How does SUMOylation fine-tune the dynamics of DNA repair mechanisms?

This project combines cutting-edge techniques and utilizes yeast and human cell models to answer these questions:

1. **Tracking of Repair Protein Association with DNA**: Using advanced molecular biology tools such as chromatin immunoprecipitation followed by next-generation sequencing and live-cell time-lapse microscopy, we aim to map how SUMOylation controls the recruitment of key DNA repair proteins (Rad51, Rad52, Ku70) at specific genomic loci in fission yeast.
2. **Innovative Technology**: We will develop a novel technique called Replication-Arrest SUMO Identification (RA-SUMO-ID). This approach combines proximity labelling and targeted DNA replication arrest, allowing us to identify SUMO-dependent proteins at specific genomic sites.
3. **Human Implications**: To explore the conservation of SUMO-mediated repair mechanisms between yeast and humans, we will investigate the impact of SUMO regulators on the recruitment of repair proteins like KU70 and RAD51 in human cells.

This project aims to reveal how SUMOylation orchestrates DNA repair under replication stress. The obtained data shall uncover unique SUMO features that may represent vulnerabilities in cancer cells. Since SUMO pathways are highly conserved from yeast to humans, our findings could pave the way for innovative cancer therapies targeting specific SUMO regulators.