This research project titled “Role of LTR-driven circTNFRSF11A in the pathogenesis of classic Hodgkin lymphoma (cHL)” examines circular RNAs (circRNAs) and their potential function in cHL, a tumor affecting the lymphatic system. Our focus is on circTNFRSF11A, which based on our preliminary data, may play an important role in the development of this lymphoma.

CircRNAs are a special type of RNA molecule that form closed loops, unlike the usual linear RNA strands. This unique structure makes them very stable and capable of playing important functions in our cells. One of their well-studied roles is acting as "sponges" for microRNAs (miRNAs). MiRNAs regulate gene expression by binding to target mRNAs, but circRNAs can bind to these miRNAs and block their function, which can significantly impact cellular processes.

Hodgkin lymphoma (HL) is a relatively rare disease, but it is the most common lymphoma affecting teenagers and young adults. It it characterized by Hodgkin and Reed-Sternberg (HRS) cells, which originate from B-cells, a type of white blood cell. This transformation is partly driven by a signaling pathway known as NF-κB, which promotes cell survival and proliferation. Upregulation of this pathway is one of the main characteristics of this disease. In cHL, a gene called *TNFRSF11A*, which is a receptor crucial for activating the NF-κB pathway is overexpressed. Our preliminary data suggest that this overexpression is caused by a specific mechanism involving long terminal repeats (LTRs), which are sequences in the genome that, when activated, can enhance gene expression. Interestingly, we found that the expression of circTNFRSF11A, derived from *TNFRSF11A* gene, might also be driven by activated LTR and play a crucial role in cHL development by interacting with miRNAs and potentially function as a miRNA sponge.

Project Goals:

1. Characterizing circTNFRSF11A: We will validate the circular structure, sequence and size of circTNFRSF11A.
2. Confirming Expression Mechanism: We aim to demonstrate that circTNFRSF11A's expression is driven by LTR activation, using advanced genetic techniques like CRISPR.
3. Functional Validation: We will inhibit circTNFRSF11A in cHL cell lines and analyze the effects on cell growth and survival, which will help us understand its role in development of cHL.
4. Identifying miRNA targets: We will identify which miRNAs interact with circTNFRSF11A using novel techniques like pull-down assays and RNA sequencing, and confirm these interactions with further tests.

Uncovering the role of circTNFRSF11A in cHL, not only enhances our knowledge about cHL biology, but it could also contribute to discovery of new, less toxic diagnostic tools and therapies. If circTNFRSF11A is found to significantly contribute to the survival and growth of HRS cells, targeting this circRNA could become a new strategy to treat cHL.