Summary of PhD thesis of Marcin Szymański, MD

The pathogenesis of endometrial cancer (EC) is multifactorial and involves a range of genetic and molecular disturbances that lead to uncontrolled proliferation of endometrial cells. Among these, particular attention is drawn to the dysregulation of regulatory proteins in the cell cycle, especially cyclins. Cyclin D1, which plays a key role in the transition of cells from the G1 phase to the S phase, has been extensively studied in the context of various cancers, including EC. Cyclin K, although less well-known, seems to play a significant role in transcription regulation and cell cycle control. This doctoral dissertation focuses on the role of cyclin D1 (CCND1) and cyclin K (CCNK) in EC, analyzing their molecular mechanisms, associations with disease progression, clinical significance, and prognostic value.

In the first study – "Assessment of Cyclin D1 Expression: Prognostic Value and Functional Insights in Endometrial Cancer: In Silico Study" – the role of CCND1 in EC progression and prognosis was analyzed. Immunohistochemical (IHC) analysis revealed nuclear expression of CCND1 in tumor tissues, varying among EC subtypes. Statistical analysis showed no significant differences in CCND1 expression between EC and histologically normal endometrial tissue, nor correlations with age, malignancy grade, or FIGO stage. However, mRNA analysis based on TCGA data revealed significant overexpression of CCND1 in EC compared to normal tissue. Functional enrichment analysis indicated the involvement of Wnt, MAPK, and ERBB signaling pathways in CCND1 dysregulation. Kaplan-Meier survival analysis showed a statistically insignificant trend toward poorer survival for patients with high CCND1 expression.

The second study – " Prognostic Evaluation and Functional Characterization of Cyclin K Expression in Endometrial Cancer: Immunohistochemical and In Silico Analysis" – focused on the role of CCNK in EC progression and prognosis. IHC analysis showed significantly higher expression of CCNK in EC compared to histologically normal endometrial tissue ($p < 0.0001$). High CCNK expression correlated with more advanced T stage ($p = 0.0499$) and higher FIGO stage ($p = 0.0433$), suggesting its involvement in tumor progression. Kaplan-Meier survival analysis indicated that high CCNK expression was associated with poorer survival, particularly in non-endometrioid EC ($p = 0.02$). *CCNK* mRNA expression was significantly elevated in this EC subtype ($p = 0.0445$), while in endometrioid EC, the differences were not significant.

Functional enrichment analysis showed that CCNK is involved in processes such as RNA metabolism, transcription regulation, and chromatin organization.

In conclusion, both CCND1 and CCNK are involved in pathways regulating the cell cycle, transcription, and DNA damage response, indicating their potential role in EC progression and treatment resistance. Both proteins could serve as potential therapeutic targets, especially in aggressive cancers with limited effectiveness of standard treatments. However, further functional and validation studies are needed to more precisely define the mechanisms of action of CCND1 and CCNK and their utility as prognostic biomarkers in EC.