Univerza v Ljubljani

CELSA
Central Europe Leuven Strategic Alliance

Project: Degradation of CDK1 and HDACs as a strategy to treat T-cell malignancies

Project duration: 1 Oct 2023 – 30 Sept 2025

Coordinator (Slovenia): Univerza v Ljubljani, Fakulteta za farmacijo

Project leader at UL FFA: izr. prof. dr. Izidor Sosič

Coordinator (Belgium): Laboratory of Molecular Biology of Leukemia (VIB-KU Leuven)

Project leader at VIB-KU Leuven: prof. dr. Jan Cools

Project summary:

Our recent studies in peripheral T-cell lymphoma (PTCL) have identified an important role for EZH2 as a transcriptional co-factor of NMYC. Our data show that this is independent of the methyltransfersase activity of EZH2 and that phosphorylation of EZH2 by CDK1 is required to stabilize NMYC and MYB. To further investigate the clinical value of these findings for T-cell leukemia and lymphoma, we have investigated EZH2 degradation and CDK1 inhibition together with the FDA-approved histone deacetylase (HDAC) inhibitors on the survival of lymphoma/leukemia cells. Our data show strong synergy between HDAC inhibitors and EZH2 degraders or CDK1 inhibitors, both in direct effect on NMYC and MYB protein levels, and on cell viability. For EZH2 we use protein degraders, because the enzymatic activity of EZH2 is not required for its transcriptional function. To target CDK1 or HDACs we used enzymatic inhibitors, but also for these targets protein degraders (PROTACs) could be of interest, as these could be more potent and less affected by resistance mutations. In this CELSA project, we aim to convert inhibitors of CDK1 and HDAC into PROTACs. We will test the activity of these PROTACs to inhibit our cell models of T-cell malignancies alone or in combination with EZH2 degraders. Moreover, we will compare the potency and specificity of these PROTACs with the enzymatic inhibitors. The results of this project will contribute to the development of more effective and less toxic treatments for T-cell malignancies.

Web page: Research Portal - Degradation of CDK1 and HDACs as a strategy to treat T-cell malignancies (kuleuven.be)