Dual cell cycle blockade and immune checkpoint inhibition as a potential strategy of sequential anticancer therapy – Alicja Słota

The human body consists of various cell types that, to maintain homeostasis, undergo a cell cycle, controlled by regulatory proteins, mainly cyclin-dependent kinases (CDKs). Certain types of cancer cells are characterized by dysregulation in cell cycle control, due to abnormal activity of these proteins, leading to uncontrolled cell division and tumor growth. The CDK4 and CDK6 proteins are well-studied and successfully used as therapeutic targets for cancer treatment. To date, three CDK4/6 inhibitors have been approved by the U.S. Food and Drug Administration (FDA) and are first-line treatments for patients with advanced breast cancer. Although inhibition of CDK activity is an effective therapeutic strategy, it often proves toxic or insufficient, as cancer cells can evade the effects of the inhibitor. In recent years, a new approach to cell cycle blocking has emerged, utilizing small-molecule compounds (PROTACs) that can induce selective degradation of the target protein. Another attempt to address resistance is the simultaneous use of a second CDK protein inhibitor, such as CDK2. Such a strategy is currently being tested in clinical trials to evaluate the efficacy and safety of simultaneously blocking CDK4/6 and CDK2 in the treatment of cancers resistant to standard therapies. Notably, in April 2025, the FDA granted Fast Track designation for the novel CDK2 inhibitor INX-315 (Incyclix Bio) as a promising therapeutic strategy for patients with advanced cancers where currently available treatments are not sufficient. Recent cancer treatment strategies increasingly focus on combination therapies that target multiple pathways to improve cancer cell elimination and reduce resistance. One promising approach combines cell cycle inhibition, which suppresses tumor cell proliferation, with immunotherapy that enhances the immune response by blocking checkpoints such as PD-1/PD-L1.

In the project, I am addressing this timely topic by planning to explore sequential therapy strategies based on simultaneous CDK2 inhibition and selective CDK4/6 degradation using PROTAC, as well as checkpoint inhibitors to increase the efficacy and immunocompatibility of the treatment. The project envisions a series of *in vitro* studies to assess the condition of tumor cells and immune cells after CDK2 blocking and CDK4/6 degrading therapies. In addition, we will use double and triple co-culture models of cells, allowing us to evaluate the efficacy of sequential anticancer therapy and study cell-cell interactions in the tumor microenvironment. The results will form the basis for further studies in more advanced animal models, filling the cognitive gap and paving the way for novel combination therapies in oncology.

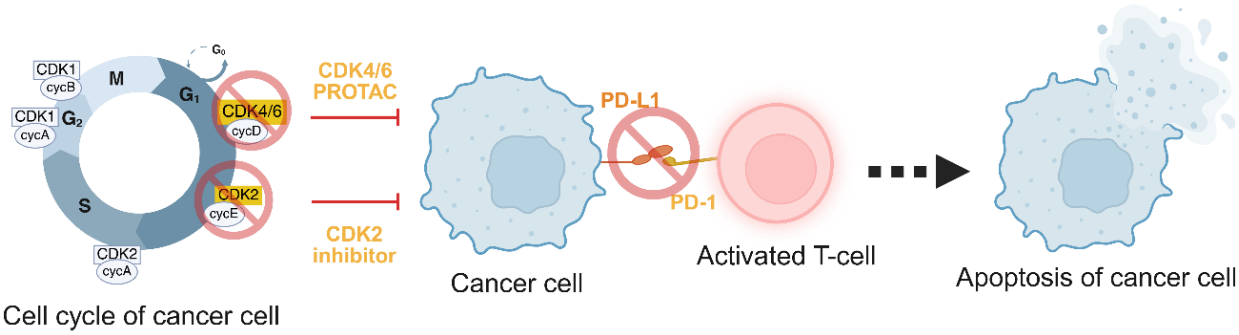

Figure 1 Antitumor combination therapy with dual cell cycle modulation and PD-1/PD-L1 immune checkpoint blockade.