Targeted Degradation of the MLL Complex in Leukemia: A PROTAC-Based Therapeutic Strategy

Leukemia is a cancer of blood and bone marrow that disrupts the production of healthy blood cells. Instead of leukocytes which protect the body against infections, the body starts producing abnormal cancerous cells. These cells multiply rapidly, crowding out healthy blood cells and weakening the immune system. Every three minutes, someone in the world is diagnosed with leukemia. In Poland, around **800** cases of acute myeloid leukemia (**AML**) are recorded each year, and all blood cancers combined account for approximately **9,000** new cases annually, making up **5.5%** of all malignant tumors in the country. Leukemia is also the most common cancer in children. Acute forms of the disease progress rapidly and can be fatal if not diagnosed and treated in time.

Why is leukemia treatment still a challenge? Thanks to advancements in medicine, many cases of leukemia can be effectively treated. However, some forms remain particularly difficult to manage. In aggressive cases, the survival rate is only **35%**. One of the most severe types is *MLL*-r leukemia (Mixed Lineage Leukemia, MLL), which: Accounts for over **70%** of leukemia cases in infants, making it one of the leading causes of cancer-related deaths in this age group. Affects **5–10%** of adult patients, where conventional treatments often prove ineffective. Standard chemotherapy frequently fails to deliver the expected results. This is why researchers are focusing on new treatment strategies that may offer a more effective approach to combating the disease.

A New Hope: Menin Inhibitors: The development of MLL leukemia is driven by mutations in the *MLL* gene, leading to the formation of drive MLL fusion proteins that cancer progression. A key player in this process is **menin**, a protein that supports leukemia development. Studies have shown that blocking **menin** can stop the progression of the disease. This has led to the development of a new class of drugs **– menin inhibitors**, which act as a **"switch"** to turn off leukemia-promoting mechanisms.

The Challenge of Drug Resistance – Why Menin Inhibitors Are Only the Beginning? Although **menin inhibitors** are promising therapy, in some patients, their effectiveness decreases over time. The reason lies in the cancer's ability to adapt, developing resistance mechanisms such as mutations in **menin** itself.

To enhance treatment effectiveness, scientists are developing two innovative strategies:

- **More Potent Menin Inhibitors** – The next generation of inhibitors is being designed to permanently block **menin**, remaining effective even when cancer cells acquire mutations.
- **Menin Elimination –** A Breakthrough Therapy – Instead of only inhibiting **menin**, researchers are utilizing **PROTAC (PROteolysis TArgeting Chimera)** technology, which not only blocks but completely removes menin from cancer cells. This could lead to longer-lasting treatment effects and a lower risk of relapse.

How Are These New Therapies Tested? Biochemical Assays – Testing how effectively new compounds bind to **menin** and inhibit its function. **Cancer Cell Studies** – Evaluating whether the new substances successfully halt leukemia progression, even in treatment-resistant cases. **Protein Degradation Analysis** – Ensuring that **PROTAC** technology efficiently eliminates **menin**. **Safety Testing** – Assessing compound stability and potential side effects before advancing to animal model studies.

Could This Be a Breakthrough for Other Diseases? Yes! Beyond leukemia treatment, this research could open new therapeutic possibilities for other cancers and diseases where **menin** plays a key role. If successful, these discoveries could revolutionize oncology by introducing a new generation of therapies that eliminate disease-causing proteins. This presents a major opportunity for patients who currently have limited treatment options.

In Summary, MLL leukemia is an aggressive cancer, particularly in infants. Standard therapies often fail, prompting the development of **menin inhibitors and menin degraders** as potentially more effective and long-lasting treatments. **PROTAC** technology could set a new direction in cancer treatment.

These new therapies offer hope where existing treatments have failed. If research is successful, thousands of patients worldwide may gain access to more effective treatments and the chance for a longer life.