Novel Immunotherapeutic Strategies: Preclinical Insights

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Acute myeloid leukemia (AML) remains a challenging disease with high relapse rates and limited long-term survival. Although immunotherapy has shown major success in other hematologic malignancies, its impact in AML has been modest. This lecture focuses on novel immunotherapeutic strategies for AML, highlighting key findings from preclinical research and including recent data from engineered natural killer (NK) cell studies.

First, the immune landscape of AML is reviewed from a preclinical perspective. AML arises in the bone marrow, where leukemia cells interact with immune cells and stromal components. Leukemia cells evade immune surveillance by downregulating antigen presentation, expressing inhibitory molecules such as PD-L1, and creating an immunosuppressive microenvironment. Mouse leukemia models and humanized mouse systems have been essential tools to study these mechanisms and to evaluate new therapeutic approaches.

Next, emerging antibody-based therapies are discussed. These include bispecific antibodies that redirect T cells toward AML cells and antibody–drug conjugates that selectively deliver cytotoxic agents to leukemia targets. Preclinical studies demonstrate effective leukemia reduction but also reveal important challenges, such as cytokine release and off-target toxicity. Immune checkpoint blockade targeting PD-1 or TIM-3 has shown limited activity as monotherapy; however, combination strategies appear more promising in experimental models.

Cellular immunotherapy represents a central focus of this lecture. CAR-T cell approaches targeting AML antigens such as CD33 and CD123 have shown strong anti-leukemia activity in preclinical systems but are limited by toxicity to normal hematopoietic cells. CAR-NK cells offer potential advantages, including reduced risk of graft-versus-host disease and the possibility of off-the-shelf manufacturing. Strategies using cytokine support and genetic engineering aim to enhance NK cell persistence and function.

We also present our recent preclinical study of IL-12–secreting CAR-NK cells for the treatment of AML. In AML models, IL-12–secreting CAR-NK cells demonstrated enhanced cytotoxic activity and improved functional persistence compared with conventional CAR-NK cells. Cytokine-supported CAR-NK cells also showed increased immune activation within the leukemia microenvironment, suggesting a dual effect on both leukemia cells and surrounding immune components.

Innate immune modulation is another promising direction. Blockade of macrophage checkpoints such as the CD47–SIRPα pathway promotes phagocytosis of AML cells. Other approaches, including STING and Toll-like receptor agonists, aim to convert AML from an immune-resistant state into an immune-responsive state. Preclinical studies suggest strong synergy when these strategies are combined with antibody-based or cellular immunotherapies.

Finally, key translational challenges are addressed, including antigen heterogeneity, immune-related toxicity, limitations of animal models, and the complexity of cell therapy manufacturing. Future directions include multispecific immune cells, gene-edited effector cells, and personalized immunotherapy based on leukemia immunophenotypes.

In conclusion, preclinical research provides critical insight into both the potential and the limitations of immunotherapy in AML. Novel antibody-based therapies, engineered immune cells, and innate immune modulators represent important future treatment strategies. Data from cytokine-supported CAR-NK cell studies further support the development of next-generation cellular immunotherapies for AML.