Natural Killer Cell-Based Immunotherapy in Multiple Myeloma

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Multiple Myeloma (MM) is the second most prevalent hematological cancer, following non-Hodgkin's lymphoma. Over the last two decades, improvements in the prognosis of patients with MM are largely due to the introduction of new drug classes in the therapeutic landscape: immunomodulatory drugs, proteasome inhibitors, and CD38 monoclonal antibodies, including Daratumumab. Despite significant clinical advancements, MM remains incurable, with most patients eventually experiencing relapse, claiming the need for efficient therapies.

CARs are synthetic antigen receptors that are composed of an extracellular antigen-binding domain and intracellular signaling domain(s). There are currently two FDA-approved CAR-T cell therapies for multiple myeloma. Both target the B-cell maturation antigen (BCMA) found on the surface of myeloma cells. While these CAR-T therapies have proven value, one of many side effects includes cytokine release syndrome, in which cancer cells hyperactivate CAR-T cells, leading to an overwhelming production of cytokines. In addition, all currently approved CAR-T therapies for hematological malignancies are administered in the autologous setting, requiring the CAR-T cells to be manufactured from the patient's own cells. To address these limitations, we aim to develop a CAR-NK cell therapy for multiple myeloma as an "off-the-shelf" solution. NK cells are innate cytotoxic lymphocytes central to anti-tumor responses and are a promising source for CAR therapy, as they are not known to cause severe GvHD. This approach could potentially make CAR-NK therapy more effective, accessible, and affordable while reducing risks commonly associated with CAR-T cells. Despite increasing interest in using NK cells in adoptive cell therapies, a significant challenge regarding the CAR-NK cell quality persists: NK cell dysfunction and exhaustion. This condition, characterized by impaired NK cell function due to prolonged activation or excessive stress, presents a major obstacle for NK therapies. Developing strategies to address dysfunctional NK cells is crucial for enhancing the durability and therapeutic potential of CAR-NK therapies.

In our study, NK cells were isolated, expanded via feeder-cell stimulation, and engineered to express α-BCMA-CAR with IL-15 co-expression using lentiviral vectors. In the xenograft model, both α-BCMA-CAR and IL-15 expression were required to restrict MM growth in the blood and bone marrow. Despite near-complete and sustained elimination of MM in the bone marrow, long-term assessment of mice treated with α-BCMA-CAR-IL-15 NK cells revealed the emergence of extramedullary disease (EMD) in the form of nodal BCMA-positive MM plasmacytomas. This study showcases α-BCMA-CAR-IL-15 NK cell therapy as a potent anti-MM therapeutic, achieving sustained MM elimination from the bone marrow and greatly extending survival. However, α-BCMA-CAR-IL-15 NK cells appeared ineffective at eliminating extramedullary disease. By demonstrating the strengths and weaknesses of α-BCMA-CAR-IL15 cells, we hope this study will help direct the use of such therapies in clinical trials and provide a valuable pre-clinical MM model for studying and developing interventions for aggressive MM-EMD. We are currently dissecting mechanisms underlying EMD progression, establishing improved CAR-NK platforms, and laying the foundation for effective, scalable immunotherapies against aggressive MM subtypes.

Together, we are advancing CAR-NK therapy for multiple myeloma while establishing a clinical-grade pipeline of off-the-shelf treatments, thereby enhancing the safety, durability, and accessibility of this innovative approach for patients.