세미나 초록

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발표 주제	A CAR-Enhancer Platform to Improve the Efficacy and Durability of CAR-T cell Therapy
발표 내용	Chimeric antigen receptor (CAR) T-cell therapy has revolutionized the treatment of hematologic malignancies, yet relapse, particularly in multiple myeloma, remains a major challenge due to limited CAR-T persistence. Here, we develop IL-21-based CAR-Enhancers (CAR-E), fusion proteins comprising B-cell maturation antigen (BCMA) and a low-affinity IL-21 variant designed to selectively stimulate BCMA-directed CAR-T cells without off-target activation. Engagement of IL-21 CAR-E induces robust STAT3 phosphorylation, driving sustained CAR-T expansion, enhanced cytotoxicity, and durable tumor regression across multiple challenging tumor models. IL-21 CAR-E generates a distinct population of high-quality CAR-T cells that resist exhaustion, re-expand upon tumor rechallenge, and mediate long-term remission. Notably, IL-21 CAR-E preferentially expands $CD8^+$ and $CD4^-CD8^-$ CAR-T subsets associated with persistence. Mechanistically, this effect is entirely dependent on the 4-1BB co-stimulatory domain, revealing an unexpected integration of JAK/STAT and 4-1BB signaling that occurs independently of tumor antigen and is triggered solely by IL-21 CAR-E through juxtaposition of IL-21R and 4-1BB. Compared with IL-2-based enhancers, the IL-21 variant achieves comparable potency but superior selectivity in humanized mice, with a strong bias toward $CD8^+$ CAR-T cells and the emergence of $CD4^-CD8^-$ double-negative subsets. Together, these findings establish IL-21 CAR-E as a highly selective and durable CAR-T potentiator that rewires and integrates cytokine-costimulatory signaling to sustain long-term antitumor immunity.