Next-Generation Effector Cells in Myeloma Immunotherapy

Hyunsoo Cho
Seoul National University Hospital, Seoul, Korea

Immunotherapy for multiple myeloma (MM) is rapidly evolving beyond classical CD8 T-cell paradigms toward harnessing next-generation effector populations that can overcome marrow immunosuppression. I will present three complementary lines of work: (i) adaptive NK cells, a memory-like NK subset with low CD38 that resists daratumumab-induced fratricide and drives potent ADCC, highlighting a biomarker-guided path to optimize anti-CD38 therapy in newly diagnosed MM (Clin Cancer Res, 2021), (ii) soluble MIC (sMICA) neutralization, demonstrating that clearing sMICA restores NKG2D expression and cytotoxicity of patient NK cells ex vivo, nominating MIC-targeting antibodies as enablers of NKG2D-dependent cellular therapies (JITC, 2024), and (iii) NKG2D+ CD4 cytotoxic T cells (CD4 CTLs), a clonally expanded marrow T-cell state that directly kills myeloma via NKG2D and correlates with improved survival, defining a novel effector axis for redirection and combination strategies (Blood, 2025).

Collectively, these data outline an integrated NKG2D-centered framework in which adaptive NK cells and CD4 CTLs serve as complementary effectors whose function is potentiated by removal of soluble NKG2D ligands. The talk will propose clinically actionable concepts: selecting/expanding adaptive NK cells for anti-CD38 regimens, incorporating MIC-clearing antibodies to rescue NKG2D signaling, and engineering/redirecting CD4 CTLs to broaden responsiveness and durability of T-cell therapies. We will discuss translational trial designs, biomarker readouts (adaptive NK frequency, sMICA levels, NKG2D+ CD4 CTLs), and combination schemas with bispecifics/CARs to advance MM immunotherapy into the next generation.